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Imprinting and critical periods in early development

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The review addresses the fundamental process of 'imprinting'. In his classical studies on newly hatched goslings Konrad Lorenz analysed the development of social binding and established the term 'imprinting' to describe this process. One of his major ideas was that imprinting occurs in 'critical periods', which are limited and severely restricted to the animal's very early life. For some time past, the term 'imprinting' is also used for an epigenetic mechanism, the 'genomic imprinting', which can be simply defined as gamete-of-origin dependent modification of genotype. Furthermore, in the course of the perinatal period 'imprinting' of physiological control systems occurs. Functional systems of the organism develop from open loop systems without feedback control into closed systems controlled by feedback mechanism. During 'critical periods', the actual environment influences the development of the respective physiological control systems for the entire life period, especially by changes in neuroorganization and expression of related effector genes. On the one hand, these mechanisms may cause perinatal malprogramming, which has been related to, *e.g.*, metabolic disorders and cardiovascular diseases during later life in humans as well as in animals. On the other hand, knowledge on these mechanisms might be specifically used to induce long-term adaptation of the organism, for instance, to the postnatal climatic conditions (epigenetic temperature adaptation). Furthermore, the question if 'critical period' and 'sensitive period' are synonymous or different, and problems of identifying these developmental windows are discussed. Environmental manipulation of immature physiological mechanisms may be a physiological tool for characterization of 'critical periods'.

Keywords: imprinting; malprogramming; critical period; physiological control system; epigenetic adaptation

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Introduction

'Imprinting' describes a fundamental process of life occurring during circumscribed time windows of prenatal- and postnatal ontogenesis and having lasting effects. Since about one century, however, this term has and is been used for very different mechanisms. For instance, it is used to explain the determination of social binding as well as physiological control systems related to the environment of the developing organism but also for a mechanism related to gamete-of-origin modification of the genotype (genomic imprinting). These 'imprinting' processes will be shortly described in this review, with special emphasis on 'imprinting' of physiological control systems. The circumscribed time windows during which 'imprinting' occurs are called 'critical' and/or 'sensitive' periods. 'Critical period' and 'sensitive period' are terms, which are often used synonymously. Because of a lack of respective sources we will discuss the question if 'critical period' and 'sensitive period' are synonymous or different and how 'critical periods' can be identified and characterized.

Imprinting

DEVELOPMENT OF SOCIAL BINDING

In his classical studies on newly hatched goslings Konrad Lorenz analysed the development of social binding applying the term 'imprinting' to describe this process. One of his major ideas was that imprinting occurs during 'critical periods', which are limited and severely restricted to the animal's very early life (Lorenz, 1935).

On the basis of Lorenz´ investigations the working group of Katharina Braun from the University of Magdeburg, Germany, has investigated physiological and metabolic changes in the brain related to 'filial imprinting'. For these investigations two animal models which feature a high social binding were used: a rodent (*Octodon degus*) and a chicken (*Gallus gallus domesticus*). Learning processes, including emotional experiences, during early development induces long-term changes in the pattern of synaptic contacts in respective brain areas (Bock and Braun, 1998). A lack of these processes, *e.g.* by social deprivation, has long-lasting consequences on formation, function and interaction of synapses within functional neuronal networks (Bock and Braun, 1999a; Ovtscharoff and Braun, 2001; Bock *et al.*, 2005a). These alterations are suggested to be the basis of behavioural disorders during later life (Kreppner *et al.*, 2001, Bock *et al.*, 2003, Bartesaghi *et al.*, 2006).

During early ontogenesis functional neuronal circuits develop in two phases, which are triggered by sensory input. In the first phase the number of synaptic contacts is increasing, whereas in the second phase (synaptic reorganization) their number decreases (Brown *et al.*, 2004). Only those contacts remain which are necessary, for instance, to maintain homeostasis or to process emotional signals under the respective surroundings and which repeatedly receive sensoric inputs (Bock *et al.*, 2003). Altogether, the increase in the number of synaptic contacts during the first phase, as well as their reduction during the second phase need sensory (social / environmental) stimulation. Bock and Braun (1999b) have shown that in comparison to 7-day-old social deprived domestic chicks, 'filial imprinting' induced synaptic pruning in higher associative forebrain areas. In 'filial imprinting' the glutamergic system plays an important role. Glutamate activates *N*-methyl-$_D$-aspartate (NMDA)-receptors, which are particularly important for learning and memory. In chickens, blockage of these receptors suppresses learning induced elimination of synaptic contacts (Bock and Braun, 1999a). Another system which alters the emotional and motivational status of the animal during 'filial imprinting' seems to be the μ-opiate

receptor-mediated modulation of serotonergic and dopaminergic neurotransmission (Baldauf *et al.*, 2005). At the molecular level neuronal plasticity induced by learning processes is characterized by a rapid up-regulation of the de novo RNA and protein synthesis, which is mediated by the activation of immediate early genes. In 1-day-old chicken after 30 min of acoustic stimulation immediate early genes related to 'filial imprinting' like *ARC/ARG3.1* (activity-regulated cytoskeleton-associated protein/activity-regulated gene) (Bock *et al.*, 2005b) and zenk (Thode *et al.*, 2005) were identified to be activated. Studies in rats have shown that the level of maternal care may alter the offspring's epigenome, *e.g.* at the glucocorticoid receptor gene promotor in the hippocampus. In offspring of 'low and high care' mothers differences in the level of DNA methylation were found, induced during the first postnatal week ('critical period'), maintained into adulthood and related to stress responsibility throughout life (Weavers *et al.*, 2004).

GENOMIC IMPRINTING

During recent years, the term 'imprinting' is also used for an epigenetic mechanism, the 'genomic imprinting', which can be simply defined as gamete-of-origin dependent modification of the genotype. Epigenetic marks ('imprints') are the result of DNA and chromatin modifications in female and male germ lines and/or during, or soon after fertilisation (Li, 2002). Alterations in 'genomic imprinting' are related to various disorders during later development and life (Surani, 1998; Ferguson-Smith and Surani, 2001, Davis *et al.*, 2005). 'Genomic imprinting' has been conserved through evolution and must likely serves an important purpose in developmental biology and ontogenesis. It was mostly found in eutherians (*i.e.* placental animals) but there is also some evidence for imprinting in marsupials (O`Neill *et al.*, 2000) and flowering plants (Vinkenoog *et al.*, 2003). The question, if 'genomic imprinting' occurs also in birds, is discussed controversial. The most well-known 'parent conflict' (parental genetic 'tug-of-war') hypothesis (Moore and Haig, 1991) assumes that imprinting evolved as a result of conflicting interests between paternal and maternal genes. Paternal genes promote embryonic growth and maternal genes have the opposite effect and, therefore, conserve maternal resources. This model excludes oviparous taxa like birds from having imprinted genes, because in this species genes expressed during embryogenesis cannot influence the amount of resources they may receive from the mother. However, in the last years investigations related to 'genomic imprinting' in chicken show conflicting results. For instance, monoallelically expressed insulin-like growth factor 2 (IGF2) was found in some chicken embryos from either paternal or maternal alleles (Koski *et al.*, 2000). Other authors reported that IGF2 was biallelic expressed in chicken embryos (O´Neill *et al.*, 2000; Nolan *et al.*, 2001). Further studies show indications for the existence of imprinted genes in chicken. In the development of the ascites syndrome in broilers direct and maternal genetic effects play an important role (Pakdel *et al.*, 2002). In chicken occurrence of quantitative trait loci (QTL) with parent-of-origin specific expression could be a plausible explanation for some reciprocal effects in poultry (Tuiskula-Haavisto *et al.*, 2004). QTL with parent-of-origin specific expression seems to be the result of 'genomic imprinting'. The presence of imprinted genes could be of high interest for poultry breeding, because it could be of major importance for unequal performance in reciprocal matings between commercial lines (Koski *et al.*, 2000). Although methylation is clearly involved in imprinting processes (Li, 2002), the precise mechanisms of 'genomic imprinting' are unknown and the reason for the evolution of imprinting is not well understood (Yokomine *et al.*, 2005). 'Genomic imprinting' and 'filial imprinting' as described above, or 'imprinting' of physiological control systems as described below, might have in common, the alteration of the DNA methylation status. However, in the case of 'genomic imprinting' alterations of

the methylation status occur in very early stage of development, whereas in the case of 'filial / physiological imprinting' they are rather induced by environmental alterations during 'critical periods' of late embryonic development or early life. It has to be noted, that in this sense 'genomic imprinting' may occur independently of classical 'filial imprinting' or the 'imprinting' (programming and malprogramming) of physiological control systems, which is described in the following section.

IMPRINTING OF PHYSIOLOGICAL CONTROL SYSTEMS

Against the background summarized above our hypothesis states that, in the course of the perinatal period, also 'imprinting' of physiological control systems occurs which, moreover, probably is realized by both neural 'imprinting' at the microstructural level (*e.g.*, in terms of synaptic plasticity) as well as 'genomic imprinting' by lasting environment-induced modification of the genome. Basically, most functional systems of the organism develop from open loop systems without feedback control into closed control systems regulated by feedback mechanisms. During 'critical periods', the actual level at which physiological parameters occur may pre-determine the 'set point' ('set ranges') of the respective physiological control system during the entire life period, possibly through acquired changes in the expression of related effector genes. Determination of the 'set point' depends on the environment experienced by the embryo and foetus during 'critical periods' of development (first described as 'determination rule' by Dörner, 1974). Günter Dörner, a pioneer of developmental neuroendocrinology, developed a general etiological concept of 'epigenetic' perinatal programming of the lifetime function of fundamental regulatory systems. In this concept, hormones play a decisive role as environment-dependent organizers of the neuro-endocrine-immune system, which finally regulates all fundamental processes of life (Dörner, 1975; 1976). During 'critical periods' hormones as well as neurotransmitters and cytotokines (as immune cell hormones) are involved in differentiation, maturation and functional programming of their own central nervous controllers within the respective physiological regulatory systems. They act as critical endogenous effectors, which transmit environmental informations (*e.g.* sensible input, social interaction) to the genome. Finally, they are thereby also acting as epigenetic factors.

On the one hand, this mechanism seems to be a possible basis for perinatal malprogramming which, *e.g.*, causes metabolic disorders and cardiovascular diseases as well as behavioural disorders during later life in humans as well as in animals (examples will be described below). On the other hand, knowledge and better understanding of these mechanisms might be specifically used to induce long term adaptation of an organism, for instance, to postnatal climatic conditions (epigenetic temperature adaptation). *Figure 1* summarizes this conceptional approach.

I Perinatal malprogramming

Perinatal malprogramming occurs when epigenetic effectors are present in non-physiological concentrations. As an outstanding example, hormones can act as 'endogenous functional teratogenes' by malprogramming the neuro-endocrine-immune network. In the following, three examples are shortly addressed.

Early sex steroid levels have a long-lasting impact on reproductive function and behaviour in vertebrates. Sexual brain organization can be permanently influenced by genetic as well as epigenetic factors, such as stressful situations or 'endocrine disruptors' (Dörner, 1974, 1975, 1976; Dörner *et al.*, 2001). During 'critical periods', alterations of hormone and/or neurotransmitter levels may lead to changes in the 'imprinting' of sexual functions. In the canary a high testosterone level in the yolk induces post hatching increased aggressive behaviour in female as well as male birds (Schwabl, 1996, 1997).

Endocrine disruptors, such as the pesticide DDT or bisphenol A, are characterized by estrogenic and anti-androgenic activity. In men DDT exposure in perinatal life seems to induce a decrease in spermatogenesis (Dörner, 2002). Perinatal administration of bisphenol A causes feminisation, for instance, in *Xenopus laevis* tadpoles (Levy *et al.*, 2004) as well as in male chicken (Furuya *et al.*, 2002).

In mammals including man gestational diabetes as well as early postnatal overfeeding, leading to perinatal hyperinsulinism, may result in increased later risk of becoming overweight and developing diabetes and alterations typical for the Metabolic Syndrome, a cluster of adipogenic, diabetogenic, and cardiovascular risk factors. Elevated insulin and leptin concentrations during 'critical periods' of neuronal development may cause a malprogramming of the neuropeptidergic systems of central nervous regulatory areas of body weight and metabolism, especially in the hypothalamus (*Figure 2*). Similar changes are also possible in birds. This perinatally 'imprinted' malorganisation of central controllers and the resultant disposition to obesity and diabetes may be even passed on the succeeding generations in an epigenetic fashion (for details see Plagemann, 2004).

In mammals, foetal stress during 'critical periods', *e.g.* caused by malfunction of the uterus or placenta, can lead to moderate hypoxia and subsequently to permanent alterations of neural functions (Duncan *et al.*, 2000; van den Hove *et al.*, 2006). Furthermore, prenatal hypoxia can induce foetal growth inhibition (Jacobs *et al.*, 1988), which is linked to a higher prevalence of cardiovascular and metabolic diseases in adults (Barker, 1995). Similar effects can be seen in poultry. The ascites syndrome in poultry, which is associated with abnormally high blood pressure (pulmonary hypertension syndrome) and right ventricle hypertension, can be related to causal factors occurring already during incubation. Both symptoms are basically associated with prenatal hypoxia or hypoxemia, which are present in the air chamber of the egg at the final stage of incubation. A decrease in the time the embryo experiences hypoxia, *e.g.* by incubation in an environment with a high concentration of CO_2 (Buys *et al.*, 1998) or at high altitude (Hassanzadeh *et al.*, 2004) not only leads to earlier hatching but also to a decreased incidence of ascites during growing period. Different atmospheric pressure during incubation, for instance, interacts with the endocrine function of the embryo. It changes the plasma triiodothyronine (T_3), tetraiodothyronine (T_4) concentration, the T_3/T_4 ratio as well as the lactic acid and corticosterone levels (Hassanzadeh *et al.*, 2004). In the pathogenesis of cardiovascular diseases hyperactivity of the sympathetic nervous system plays an important role. Sustained increase in sympathetic activity is possibly linked to chronic activation of hypothalamic paraventricular neurons, which can be induced by chronic stress, chronic activation of peripheral receptors and increased levels of circulating factors, such as angiotensin II or cytokines (Dampney *et al.*, 2005). Ruitenbeek *et al.* (2000) have demonstrated that chronic hypoxia during chick incubation stimulates adrenal catecholamines release and synthesis and causes sympathetic vascular hyperinnervation, which leads to functional changes of arterial smooth muscle cells, sympathetic innervation and endothelium in post-hatched chickens. Furthermore, after chronic prenatal hypoxia reduction of total body weight was observed, which is in agreement with studies in mammals including man.

II Epigenetic temperature adaptation

Knowledge on 'imprinting' of physiological control systems might be specifically used to induce long-term adaptation of an organism like, for instance, to the postnatal climatic conditions. For an 'imprinting' like that of the thermoregulatory system the term 'epigenetic (temperature) adaptation' was introduced (Nichelmann *et al.*, 1994, 1999; Tzschentke and Basta, 2002; Tzschentke *et al.*, 2004). In chicken and other precocial birds epigenetic temperature adaptation can be induced by changes in incubation temperature at

the end of embryonic development (Decuypere, 1984; Minne and Decuypere, 1984; Nichelmann *et al.*, 1994; Tzschentke and Nichelmann, 1997; Tzschentke and Basta, 2002, Loh *et al.*, 2004) as well as by thermal conditioning during the first days after hatching (Yahav and Plavnik, 1999; Yahav, 2000). Altogether, prenatal temperature experiences induce postnatal warm or cold adaptation (*Figure 3*). The change in the levels of heat production in differentially incubated birds occurs already before hatching (Loh *et al.*, 2004). On the first day of post hatching Muscovy ducklings incubated at lower temperatures than normal, for instance, have a 56% higher heat production and a higher deep body temperature under cold load as compared to controls (1 hour at 10°C). Cold incubated birds are able to control their actual deep body temperature at this set-point, in contrary to those incubated at 37.5°C, which display a lower heat production. Minne and Decuypere (1984) found that cold incubated chicken had a higher heat production over a range of ambient temperatures up to 8 weeks of post-hatching. The higher heat production was accompanied with higher T_3 and T_4 levels. In a temperature gradient, Muscovy ducklings incubated at a low temperature preferred a significantly lower temperature than birds incubated at the normal incubation temperature during the first 10 days of post-hatching. This supports the hypothesis that avian prenatal cold experience leads to a downward shift of the thermoregulatory set-point (Tzschentke and Nichelmann, 1999). On the other hand, the preferred ambient temperature in 1- to 10-day-old turkeys is higher after a prenatal heat load (38.5°C) than in birds incubated at the normal temperature (37.5°C). This indicates an elevation of the thermoregulatory set-point after prenatal heat load. Changes in the thermosensitivity of the control centre of the thermoregulatory system reflect the changes in peripheral thermoregulatory mechanisms after prenatal temperature experiences. In Muscovy ducklings, during the first days of life changes in incubation temperature induced a clear alteration of neuronal hypothalamic thermosensitivity (Tzschentke and Basta, 2002). On the 10th day of post-hatching it could be observed that prenatal cold load elevated the neuronal hypothalamic warm-sensitivity, with an increased proportion of warm and a reduced proportion of cold sensitive neurones in comparison with the control group. Prenatal warm load induced the opposite effect (*Figure 3*).

Critical and sensitive periods: synonymous or different?

The terms ‘critical period’ and ‘sensitive period’ are often used synonymously. There is, however, a lack of sources for a clear distinction between both periods. According to Bailey (2001) and Bailey *et al.* (2001), a ‘critical period’ has to be considered the time during which a certain experience necessarily must occur to enable development to proceed normally. It begins and ends rather abruptly. A ‘sensitive period’ is a period of “maximal” sensitivity, *e.g.*, when a child is especially receptive to certain kinds of environmental experiences. It begins and ends rather gradually. A classical example for the necessity that certain experiences have to occur in specific time windows during early ontogensesis is the development of eye-dominance columns in the mammalian cortex, which is exclusively related with sensory input during the ‘critical period’ (Ferster and LeVay, 1978; Brown *et al.*, 2004). In monkeys, for instance, deprivation of sensory input during the first 6 months of postnatal development is followed by visual losses (Hubel and Wiesel, 1977). Therefore, processes like ‘imprinting’ of social binding, postulated by Konrad Lorenz, and of physiological systems, as inaugurated by Günter Dörner, occur during ‘critical periods’ in terms of circumscribed time windows in the course of early development. On the one hand, during these periods certain experiences definitely must occur to ensure development of physiological control systems to proceed normally. On the

other hand, suboptimal environmental conditions therefore can ultimately lead to abnormal experiences, which can induce long-lasting malprogramming of the respective systems as a basis for later diseases or behavioural disorders. It is therefore suggested here to use the term 'critical period' different from the term 'sensitive period', as the latter can occur, even repetitively, throughout the whole life span and is not necessarily characterized by irreversibility of the 'programmed' effect.

PROBLEMS OF IDENTIFICATION AND CHARACTERIZATION OF 'CRITICAL PERIODS'

It is very difficult to determine 'critical periods', because time and duration are species-specific as well as system-specific. For instance, during development of the primate visual system for each specific visual function different and partially overlapping 'critical periods' were found (Harwerth *et al.*, 1986).

For identification of 'critical periods' a useful tool seems to be environmental manipulation of immature physiological mechanisms. Regularities of early development of physiological control systems, which were postulated from investigations using the bird as a model, were published earlier by Nichelmann *et al.* (2001), Tzschentke and Basta (2002) and Tzschentke *et al.* (2004):

The activity of organ functions occurs during embryonic development before this function is ultimately necessary to ensure the survival of the embryo. Prenatal activation of some functional systems may have a training effect on the postnatal efficiency.

During early ontogenesis most body functions start with uncoordinated or proximate non-adaptive reactions on environmental influences.

During the prenatal period, epigenetic adaptation mechanisms adapt the organism for the expected postnatal environmental conditions.

Regularity (2) summarizes a typical reaction pattern of physiological systems during early ontogeny. Environmental manipulations during the prenatal or early postnatal phase first lead to uncoordinated and almost non-adaptive reactions of the respective physiological control systems. The theory is that during early ontogenesis of body functions it seems not to be important for the organism that a distinct adaptable reaction on various environmental influences occurs, but rather that any reaction occurs seems to be important for the adaptability during the later life (*training effect*). These proximate non-adaptive reactions become coordinated and adaptive during later development, probably with closing of the regulatory system. For instance, experiments at the end of incubation time in chicken embryos revealed first proximate non-adaptive and later adaptive reactions with respect to the influence of cooling and warming on blood flow in the vessels of chorioallantoic membrane (Nichelmann and Tzschentke, 2003). In chicken embryos the blood flow increased or decreased while warming or cooling at day 15 until day 19 of incubation (proximate non-adaptive). After this period, the reaction became proximate adaptive; at day 20 and 21 of incubation, the blood flow in the chorioallantoic membrane increased during warming and decreased during cooling, as expected (*Figure 4*). Similar changes in the blood flow during cooling or warming were also found in Muscovy duck embryos at the end of incubation (Tzschentke, 2002). This characteristic reaction pattern could be a physiological tool, which helps to characterize a 'critical period' of the respective system during the course of early development, where regulatory systems develop from an open loop system without feedback into a closed control system with feedback.

Summary and conclusion

Imprinting of social behaviour and 'imprinting' of physiological control systems are fundamental processes of life. During 'critical periods' of development the actual natural and social environment has a notable impact on long-lasting determination of the respective system, organism, and individual, especially induced by acquired changes in neural organization and expression pattern of related effector genes (functional/epigenetic perinatal programming). Suboptimal and altered environmental conditions may induce a malprogramming of respective functions, which could be the basis of diseases and disorders during the entire life time (embryonic/foetal/perinatal origin of adult diseases). To protect organisms from malprogramming, more detailed knowledge on mechanisms of 'imprinting' is necessary. However, a main problem will be to identify and characterize 'critical periods' for the respective systems, because time and duration of these depend on species and systems affected while, moreover, concrete functions even within a species and physiological system may have different 'critical periods'.

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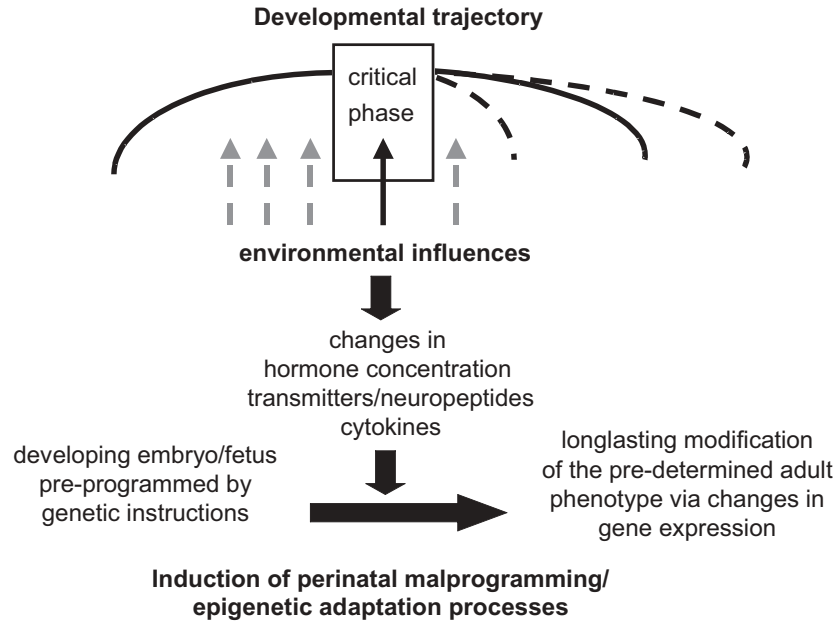

Figure 1 Induction of epigenetic perinatal malprogramming or epigenetic adaptation processes, such as epigenetic temperature adaptation by environmental factors during 'critical periods' of early development.

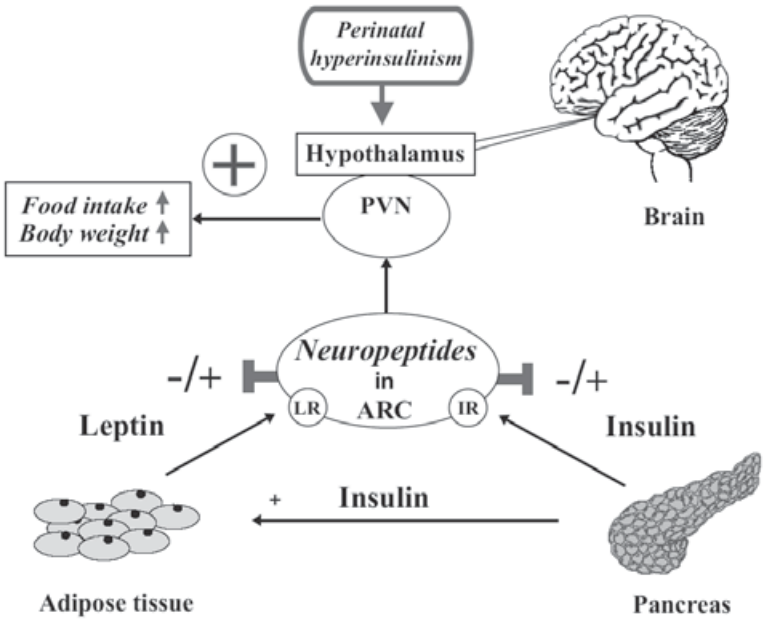

Figure 2 Exemplary mechanism of perinatal neuroendocrine 'malprogramming'. A temporary hyperinsulinism during 'critical periods' of early development may result in a kind of persisting resistance (increased threshold) to the circulating satiety signals insulin and leptin in neuropeptidergic hypothalamic regulatory systems, leading to a perinatally acquired obesity disposition. PVN – *Nucleus paraventricularis*; ARC – *Nucleus arcuatus*.

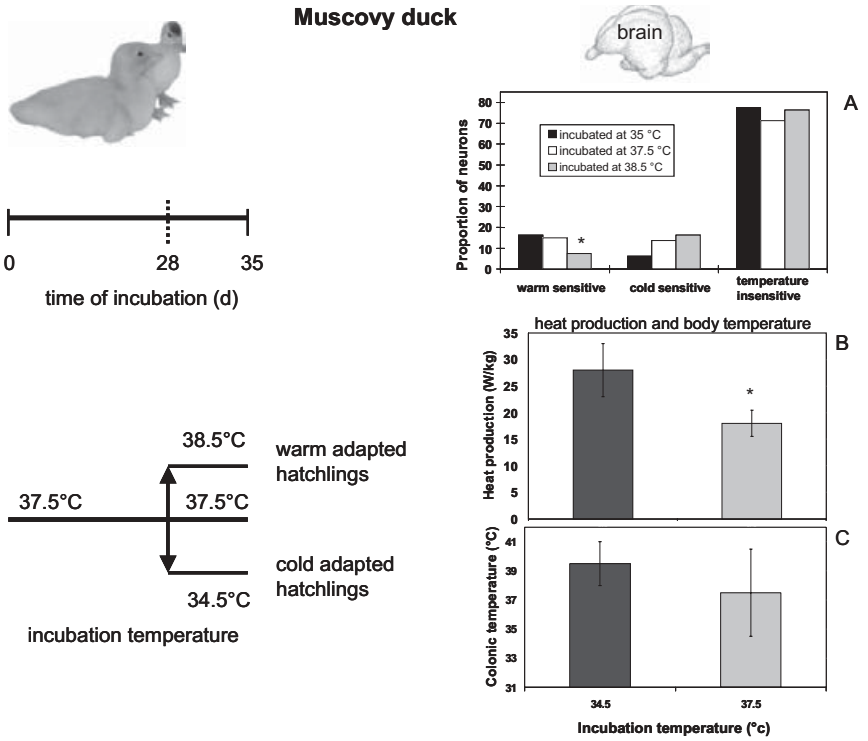

Figure 3 Epigenetic temperature adaptation in the Muscovy duck. Embryos were incubated from day 28 of incubation until hatch by warmer or colder temperatures than the usual 37.5°C.
A: Changes in the neuronal hypothalamic thermosensitivity at day 10 post-hatching were induced by changes in the incubation temperature (significant differences, χ^2-test, ($p<0.05$). For characterization of the neuronal hypothalamic thermosensitivity the proportion of warm sensitive, cold sensitive and temperature insensitive neurons in the PO/AH was determined in relation to all neurons (n = 80 neurons) investigated in the respective incubation group (Tzschentke and Basta, 2000).
B: Heat production and C: Colonic temperature in cold (34.5°C) and normal (37.5°C) incubated hatchlings after 1 h cold load of 10°C (significant differences, t-test, *$p<0.05$).

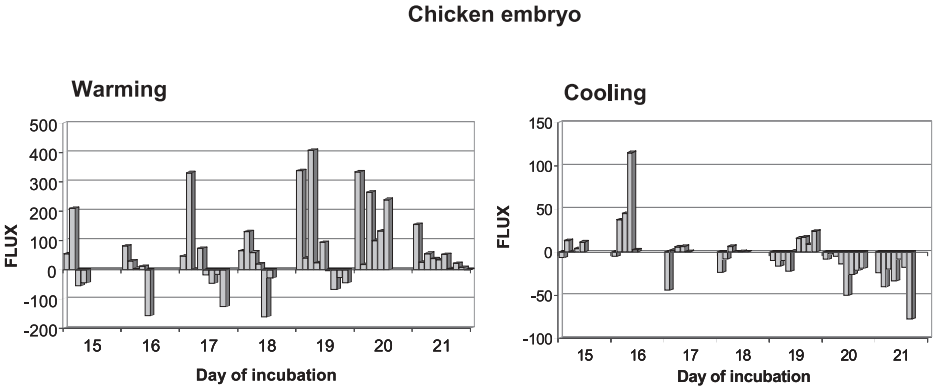

Figure 4 Influence of warming (38.5°C) and cooling (35.5°C) on blood flow in the chorioallantoic membrane of 15- to 21-day-old chicken embryos. Each column represents the reaction in one individual embryo, expressed in Flux, which is given in arbitrary units. The blood flow was measured using the Laser Doppler method (Nichelmann and Tzschentke, 1999, 2003).