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Review article

Is the brain hormonally imprintable?

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Abstract

Hormonal imprinting develops at the first encounter between the target hormone and its developing receptor in the perinatal critical period. This determines the binding and response capacity of the receptor-signal transduction system and hormone production of cells for life. Molecules similar to the hormone and excess or absence of the target hormone cause faulty imprinting with lifelong consequences. Prenatal or neonatal imprinting with opiates, other drugs and prenatal stress have harmful consequences on the adult brain. Perinatal imprinting with endorphin or serotonin decreases the serotonin level of the brain while increasing sexual activity and (as in the case of endorphin) aggression. Endorphin or serotonin antagonist treatment at weaning (late imprinting) also significantly reduces the serotonin content of the brain. Backed by literary data, these observations are discussed, and the possible consequences of medical treatments are shown. The paper concludes that an excess of molecules produced by the brain itself can provoke perinatal imprinting, and it points to the possibility of late imprinting of the brain by receptor level acting agents, including a brain product (endorphin).

Keywords: Serotonin; Endorphin; Drugs; Hormonal imprinting; Perinatal imprinting; Late imprinting

1. The biological basis of hormonal imprinting: an introduction

In the early 1970s of the last century it was observed that the unicellular Tetrahymena reacts to the hormones of higher vertebrates, keenly selecting between related molecules [1–3]. After the first encounter between a signal molecule (hormone) and the protozoan, hundreds of its progeny generations remember the meeting, reacting more sensitively to the hormone in case of further encounters [4–8]. This phenomenon won the name of *hormonal imprinting,* originally labelling the appearance of durable, transgenerational receptor memory in unicellular animals [7]. It was suggested that the phenomenon of imprinting has evolutionary importance, as the progenies of the imprinted cell more easily differentiate between useful and harmful molecules (escaping from the harmful and attracted by the useful ones). This is advantageous for the maintenance of the species while participates in the evolution of the receptor–hormone system. Later, considering that the protozoa possess not only receptors for hormones but also many vertebrate, hormone-like molecules [9,10], other characteristics of imprinting were also cleared, among them the altered hormone producing capacity of the imprinted cells [11,12].

Basic biological (developmental) processes present at a lower level of phylogeny were exerted at a higher level as well (Haeckel's law). Given this law, it seemed to be likely that hormonal imprinting took place in invertebrates [13] and in mammals as well. In rats, imprinting was demonstrated in the perinatal critical period, when a hormone first meets its developing target receptor [7]. Under the effect of the encounter between the appropriate hormone and its receptor-signal transduction system, the latter accomplished its development and reached the binding and response capacity characteristic of an adult age. The information of imprinting was transmitted to the progeny generations of imprinted cells [14–16]. Without imprinting, the receptor-signal transduction system

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remained immature, and its binding capacity different from normal [17]. However, in this period of life, the receptor's ability to select between hormones and related molecules is not complete; it can consequently bind to molecules similar to the target hormone (other members of the same hormone family, synthetic hormone analogues and drugs, certain environmental pollutants) and an excess of the similar molecules as well, as the excess of the target hormone disturbs the normal development of the receptor–hormone connections [15,16]. In these cases, *faulty imprinting* develops, along with lifelong consequences: the receptor binds to either more or less hormones than normal, and the response of the cell is altered. As the effect not only influences the acute function of the receptor-bearing cell but is also prolonged to later times, faulty imprinting has lifelong consequences on morphological, biochemical, and sexual behavioral [16,18–25] parameters, causes disturbances in genetic regulation (e.g. the persistent induction of genes [26]), and also permanently alters receptor binding and hormone levels.

Though hormonal imprinting appears physiologically during the neonatal critical period, it can also be provoked later in some special tissues and cells [15,16] at weaning and at adolescence and adult age. This is explained by the fact that hormonal imprinting is not a time-specific process but a developmental-biological, stage-specific phenomenon. For its triggering an 'open window' is needed during the period of cell differentiation, meaning that cells in continuous differentiation can also be imprinted in adults. These are the differentiating cells of the bone marrow and lymphoid organs (e.g. thymus), as well as those in the phase of regeneration. The effect of this 'late imprinting' is as longlasting as in case of the perinatal imprinting.

The molecular mechanism of hormonal imprinting has not been clarified until now. The most likely theory is based on methylation. Methyl groups on the cytosine of DNA can block transcription, and this seems to be one of the tools by which the developmental (genetic) determination of a cell takes place. It is thought that hormonal imprinting causes a rearrangement of the methylation pattern of genes [16,27,28].

Considering the influential effect of hormonal imprinting on hormone-production in the unicellular Tetrahymena, it was recently demonstrated that hormonal imprinting in mammals influences not only the development of receptors, but also the production of the imprinter hormone—if the receptor-bearing cell has this capacity at all, and if there exists cross-imprinting between chemically or functionally related imprinters. The hormone production of bone marrow-originated immune cells was studied, showing evidence of this phenomenon [29,30]. The question is whether the brain—which, although possessing differentiated cells is still able to learn and remember—can be imprinted or not. If the answer is yes, then what are the consequences?

2. Imprinting of the brain

2.1. Imprinting-like effects in connection with the brain

Imprinting-like effects on the brain were studied earlier; since the experiments of Barraclough [31] it has been known that hormonal influences are needed for the normal adjustment of sex, and that neonatal hormone level differences can cause abnormal sexuality in adults [32,33]. Other experiments dating from as early as 1988 show that aggressive behavior and sexual deviation in adults was provoked by prenatal stress, and that their opiate sensitivity as well as their analgesic responses were altered [34–37]. Prenatal stress also eliminated gender-related differences in the volumes of neuron nuclei of the suprachiasmatic nucleus [38]. Prenatal or perinatal diazepam exposure affected beta-adrenergic receptors in the cortex, the striatum and the hypothalamus [39], caused the stress-induced activation of the mesotelencephalic dopamine system [40], and affected the binding capacity of the low affinity $GABA_A$ receptors of the hypothalamus [41].

A special chapter of these observations discuss the effects of perinatal drug abuse on the different structures and functions of the brain. Prenatal exposure to morphine reduces the density of females' mu opioid receptors in an adults' hypothalamus and preoptic area by about 25% [42]. Prenatal morphine treatment alters the content and turnover of nerepinephrine in specific regions of the adult brain independently of sex [43], and modifies the development of norepinephrine and dopamine neurotransmitter systems in the hypothalamus, the preoptic area, the striatum and the cerebellum in a sexually dimorphic manner [44]. In mice, prenatal exposure to heroin induced global hyperactivation both pre- and postsynaptically along the septohippocampal cholinergic innervation [45]. Fetal or neonatal exposure to opiates as well as cocaine can cause an overall inhibition of brain growth and development [46]. Prenatal cocaine exposure selectively affects depolarization-evoked dopamine release [47] and inhibits nonassociative learning [48]. Perinatal exposure to a cannabinoid affected motor behavior in adults [49] and disturbed gene expression [50]. On their own or together, stress and drug abuse could cause perturbations of the neurotransmitter system [51]. In addition, some of its effects were supposed to be transgenerational; e.g. F_1 progenies of neonatally morphine-treated rats experienced delayed growth [52].

These observations do not, however, demonstrate the biochemical events in the brain to be a consequence of imprinting, and they do not show what happens in the case of the imprinting done after the perinatal critical period. In these experiments, foreign molecules were employed perinatally—regardless of how the receptor level was acting—in order to provoke change in adults. The results do not show what the situation is in the case of an excess of physiological molecules.