Postnatal development of adrenergic and cholinergic sensitivity in the isolated rat atria

Anneli Nukari-Siltovuori

Zoophysiological Laboratory, Department of Biology, University of Turku, SF-20500 Turku 50 (Finland), 2 June 1977

Summary. The sensitivity to adrenergic drugs in isolated rat atria increased with the postnatal development. The cholinergic chronotropic sensitivity did not further change after birth.

In the rat it has been estimated by histochemical studies that the adrenergic innervation of the heart is sparse at birth and is completed between the 21st and 50th day of life[1-3]. The ability of the rat heart to accumulate H^3-noradrenaline develops rapidly between the 6th and 15th day after birth until the adult level is reached at about 36 days[4-6], and the resting heart rate increases to a maximum within 21 days[7]. Hall[8] has found that the 11.5-day-old heart of the embryonic rat responds to adrenergic and cholinergic drugs.

The purpose of the present work was to study the sensitivity changes of the isolated atria to adrenergic and cholinergic drugs in young and adult rats.

Material and methods. The isolated atria of 148 Sprague-Dawley male rats were examined. Age groups of 1–2 days, 8–9 days, 18–19 days and 2–3 months were used. The rat weights were 8.2 ± 0.2 g, 16.0 ± 0.7 g, 29.5 ± 1.8 g and 267.0 ± 20.0 g, respectively. Rats were killed by decapitation and the hearts were dissected and rinsed in Tyrode's solution at 24 °C. The atria were mounted in a 30 ml organ bath containing Tyrode's solution gassed with 95% O_2/5% CO_2. Atria were placed with the hooks in the horizontal plane with a tension of 600 mg for the adult atria and a tension of 300 mg for the younger ones. After a stabilization period of 30–50 min, the cumulative dose-response curves for the chronotropic response to isoprenaline, Isuprel (ISO), phenylephrine, Neo-Syneprine (PHE), noradrenaline (NA), acetylcholine (ACh) and carbachol (CCh) were determined by using atria at 37 °C[9]. Only 1 dose-response curve was determined with each atria. The chronotropic responses were recorded with suction electrodes in a 4-channel Mingograf recorder. Statistical significances of the pD_2-values and the mean responses at different concentrations were calculated by Student's t-test.

Results. The base rates of the isolated atria were very similar in each of the age groups; in the adult rats 229 ± 7, in 1–2-day-old 224 ± 6, in 8–9-day-old 232 ± 8 and 18–19-day-old 242 ± 5 beats/min.

The curves in figure 1 show that the responses to adrenergic drugs increased with ageing. The ISO dose-response curve of 1–2-day-old rats (figure 1, *A*) significantly differed from those of adult animals ($p < 0.05$ at the maximum response). In the other age groups, the sensitivity to ISO was increased reaching almost the adult level at

1 T. H. Schieber and R. Heene, Histochemie *14*, 328 (1968).
2 J. De Champlain, T. Malmfors, L. Olson and Ch. Sachs, Acta physiol. scand. *80*, 276 (1970).
3 J. M. Lipp and A. M. Rudolph, Biol. Neonate *21*, 76 (1972).
4 J. Glowinski, J. Axelrod, I. J. Koplin and R. J. Wurtman, J. Pharmac. exp. Ther. *146*, 48 (1964).
5 L. L. Iversen, J. De Champlain, J. Glowinski and J. Axelrod, J. Pharmac. exp. Ther. *157*, 509 (1967).
6 Ch. Sachs, J. De Champlain, T. Malmfors and L. Olson, Eur. J. Pharmac. *9*, 67 (1970).
7 D. R. Wekstein, Am. J. Physiol. *208*, 1259 (1965).
8 E. K. Hall, J. cell. comp. Physiol. *49*, 187 (1957).
9 J. M. Rossum, Archs int. Pharmacodyn. *143*, 299 (1963).

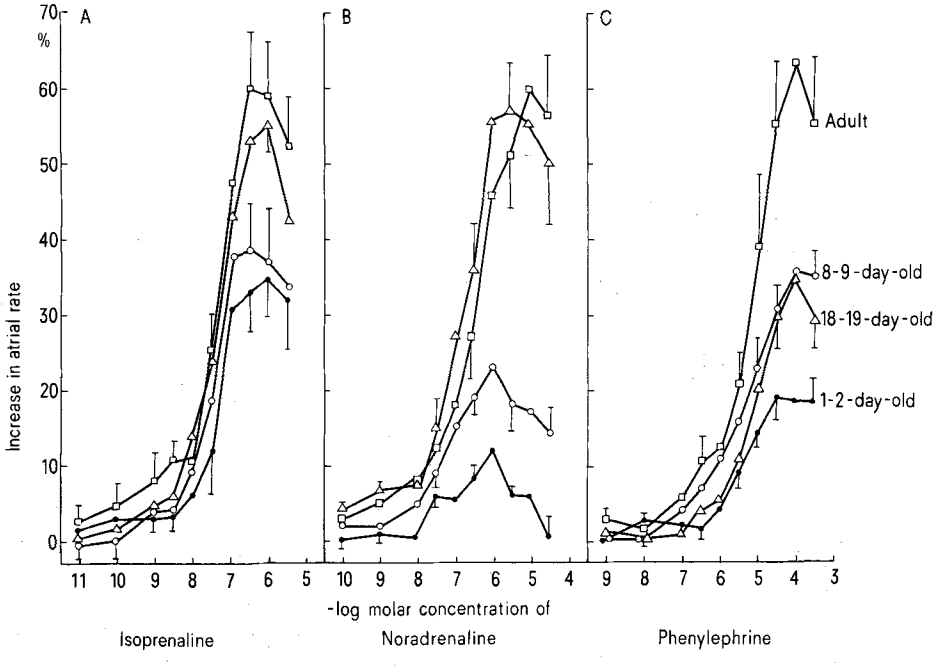

Fig. 1. Log concentration-response curves for the chronotropic responses to isoprenaline (*A*), noradrenaline (*B*) and phenylephrine (*C*) in the isolated atria from 1–2-day-old –●–, 8–9-day-old –○–, 18–19-day-old –△– and the adult rats –□–. The curves are expressed as the percentage increase from the basic contraction frequencies. The curves are the means ± SE, n = 6–10 rats.

18–19-day-old age. The similar but stronger development is to be seen in figure 1, *B*, where the maximum responses to NA of 1–2- and 8–9-day-old rats were only 20–30% from those of 18–19-days-old and the adult rats ($p < 0.001$). Responses to an alpha-adrenergic drug, PHE (figure 1, *C*), show that the sensitivity of alpha-receptors developed to the adult stage later than those of beta-receptors, the 18–19-day-old hearts still being subsensitive to PHE but not to ISO and NA.

The dose-response curves to cholinergic drugs, ACh and CCh, indicated (figure 2) that the cholinergic chronotropic sensitivity did not change significantly after birth. The responses at the different concentrations did not differ significantly between the age groups.

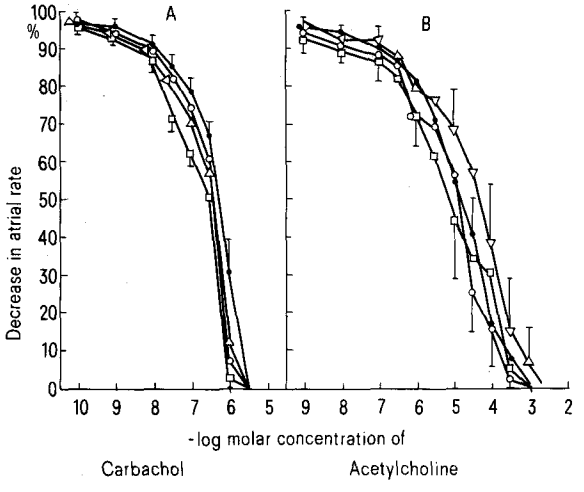

Fig. 2. Log concentration-response curves for the negative chronotropic responses to carbachol (*A*) and acetylcholine (*B*) in the isolated atria from 1–2-day-old –●–, 8–9-day-old –○–, 18–19-day-old –△– and the adult rats –□–. The results are expressed as the percentage decrease from the basic contraction frequencies. The curves are the means ± SE, n=6–8 rats.

Discussion. The present results indicated that the atrial chronotropic sensitivity to adrenergic drugs was lower in the newborn than in the adult rats. The postnatal development of adrenergic sensitivity in the atria observed in this study is well correlated to the development of the adrenergic innervation in the heart[1–3], and the development of neural uptake of H^3-NA[4–6]. Adrenergic innervation[1–3], NA uptake[4,5] and NA concentration of heart[5] increase rapidly during the 3 weeks after birth. Also the chronotropic sensitivity to ISO and NA were already developed to the adult level within 19 days, but the sensitivity to the alpha-receptor agonist, PHE, developed later. In the rat portal vein, it has been shown[10] that the sensitivity to exogenous NA increases during the first 3 weeks. The resting heart rate increases from 300 to 500 beats/min during 20 days in vivo[7] but the base rate of isolated atria did not change with age, as observed in this study and earlier by Adolph[11].

The atrial sensitivity of rats to ACh and CCh did not change further after birth, thus indicating that the cholinergic system in the rat heart is well developed at birth. Hall[8] has estimated that the embryonic heart of the 10.5-day-old rat failed to respond to ACh but hearts of 11.5–14.5-day-old rats responded by temporary diastolic arrest. Ljung and State[10] have found in the rat portal vein that the sensitivity to exogenous ACh does not increase during the postnatal development.

This study shows that there are age-related functional differences in the chronotropic responses of atria to adrenergic agonists but not to cholinergic agonists. The beta-receptor system of the rat atria appear to develop faster than the alpha-receptor system.

10 B. Ljung and D. Stage, Acta physiol. scand. *94*, 112 (1975).
11 E. A. Adolph, Am. J. Physiol. *166*, 75 (1951).

Changes of hormonal status in young mice by restricted caloric diet. Relation to lifespan extension. Preliminary results[1]

W. Pierpaoli[2]

Schweizerisches Forschungsinstitut, Medizinische Abteilung, CH-7270 Davos (Switzerland), 9 June 1977

Summary. The maintainance of mice on a reduced caloric diet for 6 weeks starting from weaning time produces persistent changes in their hormonal status as reflected by differences in blood levels of gonadal and adrenal steroids. The changes might express a permanently different hypothalamic regulation. This might account for a prolongation of their life span.

Since the discovery by McCay[3–6], it has been known for many years that a diet restricted in calories prolongs significantly the life span of mice and rats. How this operationally 'simple' procedure can effect such a remarkable prolongation of the life span is still a matter of speculation. A very important aspect which emerged from previous work was that the earlier in life the diet was instituted, the longer the animals lived.

Dilman[7] proposed in 1971 that one of the causes of senescence, and of some of its most compelling pathological manifestations (atherosclerosis, senile diabetes, increased incidence of tumors, a.o.), is an age-associated progressive elevation of the hypothalamic threshold to feed-back suppression. This might involve a compensatory increase of production and release of certain protein hormones (growth hormone, prolactin for example) which promote most of the peripheral metabolic alterations which are typical of ageing. These progressive degenerative changes of the hypothalamus were considered by him to be the cause of a kind of 'physiological' ageing; many factors of hereditary or environmental nature might powerfully contribute to the delay or acceleration of this syndrome[7].

Our work on the role of the thymus in the programming and organization of neuroendocrine functions in early ontogeny[8,9] and the notions that different kinds of manipulations can alter or affect permanently hypothalamic functions, suggested a possible mechanism by which a restricted caloric diet might prolong life. This might be by delaying and influencing the definitive organization of the hypothalamus for adult endocrine functions. The idea