# AGE CHANGES IN THE RESISTANCE OF RATS TO ADRENALIN AND SEROTONIN

I. V. Markova

Department of Pharmacology (Head – Active Member AMN SSSR V. M. Karasik), Leningrad Medical Pediatric Institute
(Presented by Active Member AMN SSSR V. M. Karasik)
Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 54, No. 12, pp. 61-63, December, 1962
Original article submitted June 24, 1961

It has been shown [1] that newborn rats are more resistant than the adults to aminasine. Because the pharmacological effects of aminasine depend mainly on its adrenolytic and antiserotonin activity, it was suggested that the high resistance of newborn rats to the drug depends on a low sensitivity of the adrenergic and serotoninergic structures.

In the present work we have studied age changes in the resistance of rats to adrenalin and serotonin.

## EXPERIMENTAL METHODS

The experiments were carried out on 350 rats of 7 ages. The adult rats were obtained from the same source. To obtain the young, pregnant rats were selected in our laboratory, and the days of birth were recorded. Adrenalin was injected intraperitoneally. Because serotonin penetrates the blood-brain barrier to a very small extent [9], 0.02-0.04 ml in physiological saline were injected into the right cerebral ventricle by means of special needles fitted with a limit device. In order to determine precisely the site of the injection, control animals received injections of physiological saline dyed with methylene blue.

## EXPERIMENTAL RESULTS

New born and one-week-old rats were much more resistant to adrenalin than adults (see table). Nevertheless, the reaction to adrenalin in them developed very rapidly: almost immediately after the injection, the skin turned pale, mobility was lost, and the animals lay on one side, or supine. When tolerated doses were injected, the rats recovered after 30-90 min, and their normal color returned. When large amounts were injected, death occurred usually after 1-3 h. At the age of two weeks the resistance of the rats to adrenalin continued to fall, and by one month it was equal to that of the adults. In all cases death occurred with signs of pulmonary edema, which was easily visible to the naked eye.

Serotonin was very toxic to the adult animals. Intravenous injection of 0.04 ml of a 1-2% solution caused respiration to cease after 1-1½ min (and immediately afterwards tonic spasms developed); the heart continued to beat for 5-7 min. We were not able to determine the lethal dose for newborn rats because the maximum attainable concentration (2% solution) was readily tolerated (out of 15 animals, not a single one died). By 1½ months, the tolerance had fallen almost to the adult level (the 2% solution caused the death of all 5 animals but none died from the 1% solution).

The effects produced by the drugs changed with age: in the newborn animals there was merely some depressant central nervous action; in the 1-week-old animals, when the suppression ceased there was a tremor, and in the 2-week-old animals, in addition, clonic spasms developed; in the 3-week-old animals there was a rotation about the longitudinal body axis towards the site of the injection. Subsequently, the suppression was less prolonged, and the excitation of the central nervous system was more intense and lasted for a longer time.

The high resistance to adrenalin and serotonin observed in newborn rats probably depends on the low sensitivity of their adrenergic and serotoninergic structures. Differences in maladies produced by treatment with serotonin in rats of different ages are clearly evidence of the different times of maturation of the serotoninergic structures and the other parts of the central nervous system. In the work of Himwich and Costa [7] it was shown that serotonin acts on

the hind parts of the brain causing a sleepy condition; it also acts on the rostral divisions causing locomotor excitation and aggressiveness. This result has led to the proposal that in the newborn rats only the serotoninergic structures of the caudal divisions of the central nervous system are developed, but with increasing age they gradually mature in the rostral divisions.

Resistance of Rats of Various Ages to Adrenalin

| Adrenalin (μg/g) | Age | | | | | | |
|---|---|---|---|---|---|---|---|
| | newborn | 1 week | 2 weeks | 3 weeks | 1 month | 1½ months | adult |
| 0,5 | — | 0/8 | — | — | 0/5 | 0/5 | 0/5 |
| 1 | 0/10 | 2/8 | — | — | 1/5 | 1/5 | 0/5 |
| 2 | — | — | — | — | — | 3/5 | 2/5 |
| 3 | 6/10 | 3/8 | 0/5 | 0/5 | 4/5 | 5/5 | 5/5 |
| 4 | — | — | 0/5 | 2/5 | 5/5 | — | — |
| 5 | 6/10 | 3/8 | 4/5 | 3/5 | — | — | — |
| 6 | — | — | 5/5 | 5/5 | — | — | — |
| 8 | — | 4/8 | — | — | — | — | — |
| 10 | 4/10 | 2/8 | — | — | — | — | — |
| 12 | — | 2/8 | — | — | — | — | — |
| 15 | 10/10 | 8/8 | — | — | — | — | — |
| $LD_{50}$ (μg/g)* | 8,1±1,14 | 9,9±1,1 | 4,1±0,61 | 4,5±0,5 | 2,0±0,3 | 2,0±0,1 | 2,1±0,3 |
| P | <0,001 | <0,001 | <0,002 | <0,001 | >0,5 | >0,5 | |

* Significance with respect to the $LD_{50}$ of adult rats.

Note: The numerator denotes the number of rats that died, and the denominator the number used in the experiment.

Because of the undeveloped condition of the hypothalamo-hypophysio-adrenal system [2, 4, 5, 8] of newborn rats, they are to be compared with adrenalectomized adult rats which have received mineral corticoids. Adrenalectomy greatly enhances sensitivity to serotonin [3] and to adrenalin [6], but newborn rats are very resistant to these substances. It may therefore be supposed that mineral corticoids which are produced in large amounts by the adrenals of newborn rats reduce the sensitivity of their serotoninergic and adrenergic structures. Confirmation is afforded by the restoration of the initial sensitivity of adrenalectomized animals to aminasine caused by the injection of bisoxycorticosterone [1]. This proposal requires further confirmation.

## SUMMARY

As we reported previously, newborn rats were more resistant to aminasine than are adult animals. Because aminasine depresses both the adrenalin and serotonin effects, we studied the resistance of rats of different ages to adrenalin and serotonin, and obtained results as follows. 1) Newborn and 1-week-old rats were more resistant to adrenalin than adults; at 2 weeks their resistance dropped sharply, and by the age of 1½ months reached the value characteristic of adults. 2) Soon after birth the rats were more resistant than were adults to serotonin injected into the cerebral ventricle; by the age of 1½ months, resistance to serotonin had fallen almost to the adult level. 3) The action of serotonin changes with the age of the animal: in newborn rats the only effect observed was a depression of the CNS; in 1-week-old animals a tremor followed the depressions, whereas in 2-week-old animals clonic-tonic convulsions occurred also; the 3-week-old rats showed a rotation about the longitudinal body axis towards the side of the injection.

## LITERATURE CITED

1. I. V. Markova, "Problems of endocrinology and hormone therapy" [in Russian], No. 8 (1962), p. 25.
2. I. A. Éskim, Pat. fiziol., No. 4 (1957), p. 10.

3. N. Canal and A. Maffei-Faccioli, Boll. Soc. ital. Biol. sper., Vol. 34 (1958), p. 787.
4. H. W. Deane, in Coll: Adrenal Function in Infants and Children. A Symposium, New York (1956), p. 4.
5. E. Endröczi, J. Szalay, and K. Lissák, Endocrinology, Bd. 34, S. 331 (1957).
6. I. Fritz and R. Levine, Am. J. Physiol., Vol. 165 (1951), p. 456.
7. W. A. Himwich and E. Costa, Fed. Proc., Vol. 19, No. 4, Pt. 1 (1960), p. 838.
8. J. B. Josimovich, A. J. Ladman, and H. W. Deane, Endocrinology, Vol. 54 (1954), p. 627.
9. D. W. Woolley and E. Shaw, Proc. Nat. Acad. Sci. (Wash.), Vol. 40 (1954), p. 228.

---

**All abbreviations of periodicals in the above bibliography are letter-by-letter transliterations of the abbreviations as given in the original Russian journal. *Some or all of this periodical literature may well be available in English translation.* A complete list of the cover-to-cover English translations appears at the back of this issue.**

---