THE IMPORTANCE OF THE PITUITARY-ADRENAL SYSTEM IN THE SENSITIVITY OF ANIMALS TO NARCOTICS AT VARIOUS AGES

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In a previous paper changes in the sensitivity of rats were described to short-acting (hexobarbital, pentothal), medium (amytal) and long-acting (medinal) barbiturates and to ether; the problem was also discussed of the importance of the comparatively low detoxication of barbiturates in the liver of animals at an early age [2, 3] in the production of the increased sensitivity of these animals to narcotics. It follows from this discussion that the age changes in the detoxicating function of the liver are not of decisive importance.

In the present article the question is examined of the relationship between the increased sensitivity of newborn animals to narcotics and the function of the pituitary-adrenal system. As we know, this system functions very inadequately in newborn animals. Endröczi and Tóth [12], for instance, believe that newborn rats are practically without an adenohypophysis, so that they do not react to different stimuli by the secretion of adrenocorticotropic hormone (ACTH).

Balfour [4] found that calves begin to react to ACTH only on the 10th-40th day after birth. According to Taylor and his co-workers [28], the elaboration and content of ACTH in the hypophysis of children are many (17) times less than in adult human subjects.

Corresponding to the failure of elaboration of ACTH there is a failure of development of the adrenal cortex. In newborn animals this is known to account for 80% of the "fetal" layer [6, 7]; the remaining 20% consists mainly of glomerular and fascicular layers. The latter appear in rats on the 16th-17th day [18], in man in the 3rd-4th months [6, 7] of intrauterine development; in the fascicular layer are produced glucocorticoids [15, 17]. In the first months of postnatal development the "fetal" layer undergoes atrophy and is replaced by the characteristic layers of the adult. The adrenal cortex of newborn animals produces very little corticoids [5-7, 11, 25, 33]. This production reaches the level characteristic of the adult animal at various times depending on the species of animal concerned (in man, for example, at 3-7 years [7]).

The importance of the pituitary-adrenal system for sensitivity to narcotics derives from work which showed that after removal of the adrenals or hypophysis from animals (mice and rats), their sensitivity to narcotics, especially to barbiturates, is sharply increased [10, 19, 24, 29, 31]. As it has been shown [19], the increased sensitivity to barbiturate depends on the fact that in adrenalectomized animals the concentration of barbiturate in the brain is significantly higher than in control animals. This may perhaps be due (or partly due) to the fact that after removal of the adrenals the permeability of the vascular wall increases [20].

After administration of cortisone or oxycortisone to adrenalectomized animals both the concentration of barbiturate in the brain and the duration of narcosis became the same as in control animals (desoxycorticosterone has no such effect). There are also reports that the glucocorticoids, and also ACTH, shorten the period of narcosis even in normal animals [31]. Consequently the cause of the enhanced sensitivity of adrenalectomized animals to narcotics is deficiency of glucocorticoids.

TABLE 1

The Effect of ACTH on the Duration of Hexobarbital and Medinal Narcosis in Rats of Different Ages

Age	Number of animals	Three daily injections of ACTH
1—3 days	60	102±3
1 week	42	101±1,5
2 weeks	32	108±20
3 »	108	75±17
1—1½ months . . .	130	118±15
2 months	40	67±25
3 »	40	52±25

Note: In Tables 1 and 2 the duration of the lateral position in the case of the control animals is taken as 100.

TABLE 2

The Effect of ACTH on the Duration of Hexobarbital Narcosis in Male and Female Rats

Age	Males		Females	
	number of animals	three daily injections	number of animals	three daily injections
3 weeks . .	20	74±19	20	92±15
1 month . .	20	122±15	20	92±6
1½ months . .	20	50±30	20	111±6
2 months . .	20	63±30	20	58±21
3 » . . .	20	37±10	20	87±10

In connection with the above, the hypothesis has been suggested that the increased sensitivity of newborn animals to narcotics depends on the insufficient development of the pituitary-adrenal system. Our investigation was for the purpose of verifying this hypothesis.

EXPERIMENTAL METHOD

Experiments were carried out on 675 white rats of different ages — from 1 day to 3 months. ACTH (in aqueous solution) was injected intraperitoneally in a dose of 5 units per 100 g body weight, either once or on 2-3 successive days. Control animals were given intraperitoneal injections of the same volume of distilled water. Sucking animals (under the age of 3 weeks) from the same litter were used both in the experiment and as controls. Two hours after the last injection of ACTH the animals were injected subcutaneously in the dorsal region with aqueous solutions of hexobarbital or medinal in doses corresponding to the age of the animals. The length of time in which the animals remained in the lateral position was determined for both the experimental and control group (in the case of the newborn animals this could be taken to mean lying supine). The duration of staying in the lateral position of the control animals was taken as 100 and was compared with the duration of the lateral position in the animals receiving preliminary injections of ACTH.

EXPERIMENTAL RESULTS

In Table 1 are given the results of the experiments in which three daily injections of ACTH were given as being the most demonstrative.

As may be seen from Table 1, the developing animals began to react to ACTH by a shortening of the period of narcosis from the age of 3 weeks, and as their development continued this effect became more and more obvious. However, it should be pointed out that rats of 1-1½ months reacted distinctively to ACTH: injection of ACTH on one or two days had practically no effect on the duration of narcosis, whereas injection for three days lengthened it considerably. This might have been connected with the fact that at this age ACTH stimulates the production of mineralocorticoids the administration of which prolongs narcosis [13, 23, 32]; it may even be used to enhance the effect of luminal and epanutin in the treatment of epilepsy [27].

If the effect of ACTH on the duration of narcosis was analyzed separately in males and females, it appeared that the males began to react much sooner to the drug and that the reaction in them was rather more pronounced (Table 2).

From data in the literature it follows that the functional development of the pituitary-adrenal system in rats terminates at the age of 3 weeks [12].

According to our findings, this was the age at which the young rats began to react to ACTH by a shortening of the period of narcosis. At this time the sensitivity of the young rats became equal to that of the adult animals to pentothal, amytal, medinal and, before long, to ether as well. The results obtained confirmed the hypothesis, mentioned above, that the increased sensitivity of newborn animals to narcotics depends on inadequate development of the pituitary-adrenal system.

This system, however, is not autonomous, but its function is regulated by the central nervous system, in particular by the hypothalamus [9, 14, 34]. As has been shown [1, 8, 16, 21, 22, 30], the central nervous system in rats reaches the characteristic adult level of development at about 2-4 weeks of life. Obviously this is the time at which the central apparatus for regulating the activity of the pituitary-adrenal system begins to function; as a result there is increased production of glucocorticoids and the sensitivity to narcotics becomes reduced.

A high content of glucocorticoids in the body, unaccompanied by the necessary development of the central nervous system cannot affect the sensitivity of the animals to narcotics. It has been shown [26], for instance, that newborn infants have a high content of maternal corticoids (which are very rapidly – by the 5th day – eliminated from the body); despite this, newborn infants are very sensitive to narcotics. The increased sensitivity to narcotics thus depends not so much on lack of glucocorticoids as on failure of development of the hypothalamo-pituitary-adrenal system as a whole.

SUMMARY

Intraperitoneal administration of ACTH shortens the hexenal and medinal narcosis in rats only from the age of 3 weeks. According to the literature data, the development of the pituitary-adrenal system in them is completed by this time. Former observations demonstrated that the sensitivity of rats to pentothal, amytal and medinal at this age (and also to ether when one month old) is equal to the sensitivity of the adult rats. The males begin to react to ACTH by a shortened period of narcosis before the females, and the reaction in the former is more pronounced. These data confirm the assumption that increased sensitivity of newborn animals to narcotics depends on the immaturity of the pituitary-adrenal system.

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