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THE SOMATOMEDINS THROUGHOUT DEVELOPMENT

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The somatomedins are a group of polypeptide hormones which act as growth and maintenance factors for a wide variety of cells. At present four such hormones have been purified from adult human plasma. These are somatomedin A (SMA) (1), somatomedin C (SMC) (2), insulin-like growth factor 1 (IGF-1) (3), and insulin-like growth factor 2 (IGF-2) (4). A closely-related polypeptide, multiplication stimulating activity (MSA) has been purified from rat liver cell conditioned medium (5).

Somatomedins are measured by bioassays and radioligand assays, specifically competitive protein binding (CPB), radioreceptorassay (RRA) and radioimmunoassay (RIA). Bioassays reflect the composite action of several stimulatory and inhibitory substances. The advantage of specificity which has been gained by the radioligand assays, particularly RIA, however, has been achieved at the expense of reflecting true biological action (Table 1). RRA, in measuring receptor binding activity, has at least maintained a stronger biological meaningfulness. None of these assays, however, are specific for any one somatomedin. The structural similarities of these polypeptides mean that they cross-react with each other in their receptors. The degree of specificity exhibited by the RIAs currently used varies according to the different antibodies. However, the somatomedins exhibit an order of potency of cross-reaction which varies according to either the receptor or antibody used. Studies in our laboratories have primarily used three radioligand assays for somatomedins whose available potency of cross-reaction is given in Table 2. The putative hormone, embryonic somatomedin, (see below) is not purified and its possible cross-reaction has been assessed by the use of fetal serum. The circulating levels of the various somatomedins have been determined throughout life in man using these different assays. Circulating levels of RIA-SMA are undetectable in the

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Table 1.

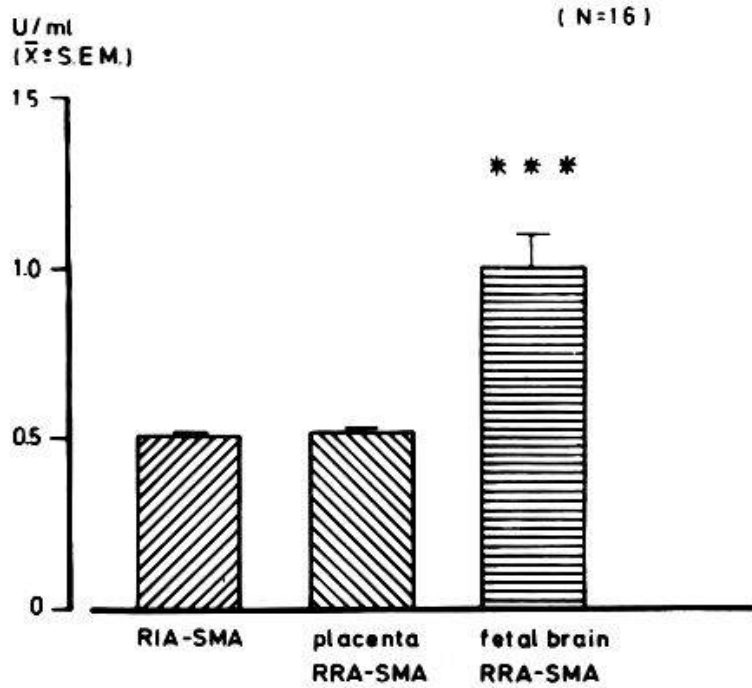
	METHODS OF MEASUREMENT		
	BIOASSAY	RADIORECEPTORASSAY	RADIOIMMUNOASSAY
BIOLOGY	+++	++	+
SPECIFICITY	+	++	+++

Table 2.

ASSAYS	OF SOMATOMEDINS		SHOWING	POTENCY	OF	CROSSREACTION
Assay	SMA	SMC	IGF-1	IGF-2	MSA	HUMAN EMBRYONIC SOMATOMEDIN
RIA-SMA	++	++	+++	+	—	—/?
placenta RRA-SMA	++	++	?	?	++	—/?
fetal brain RRA-SMA	+	?	++	++	+	++ +/?

fetus, low at birth and increase to reach adult values by approximately ten years of age (6, 7). A peak is observed at puberty but then values remain constant until approximately 30 years after which time they slowly decline. After about 70 years of age, values have fallen to those found at birth (7, 8). A similar pattern is obtained by placenta RRA-SMA except that a smaller rise at puberty is detected (8). In marked contrast, however, is the completely different pattern obtained by fetal brain RRA-SMA (6). The highest values occur in the fetal circulation where levels are increased fourfold over the adult range. The high fetal levels decline with increasing maturation. At birth, fetal brain RRA-SMA values are still much higher than those obtained by placenta RRA-SMA and RIA-SMA (Fig. 1). By two years of age, this difference has disappeared (Fig. 1). These findings led us to suggest that the fetal brain RRA-SMA detects a form of somatomedin which occurs only during fetal and possibly early postnatal life. This hormone was termed human embryonic somatomedin (6). Since RIA-SMA detects somatomedins purified from adult human plasma, we proposed that there was a switch from embryonic to adult forms of somatomedins which occurred around birth in man. By two years of age this switch appeared to be complete (6).

HUMAN CORD SERUM



HEALTHY CHILDREN 0-2 years

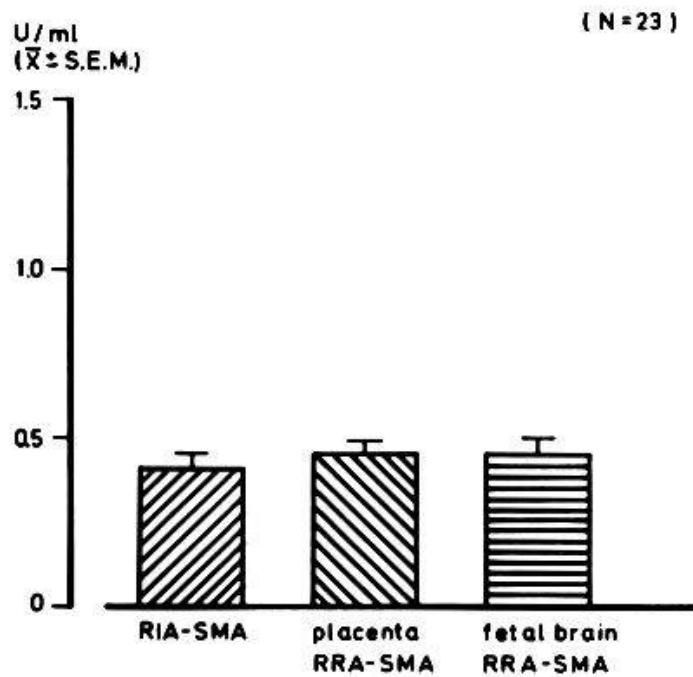


Fig. 1. Serum levels of somatomedins determined by RIA-SMA, placenta RRA-SMA and fetal brain RRA-SMA in human cord serum (upper) and children aged up to 2 years (below).
***p < 0.001

In adults, serum RIA-SMA and placenta RRA-SMA levels are regulated by growth hormone (8). A different situation appears to pertain in early life when it is unlikely that embryonic somatomedin production is regulated by growth hormone. Normal values of fetal brain RRA-SMA have been found in the only anencephalic fetus examined (6). This is in agreement with the normal body growth observed in anencephaly. Similarly in rabbits, fetal decapitation affects neither body growth nor somatomedin values (9). The importance of nutrition in early growth and the growing evidence pointing to its role as a major regulator of somatomedin production (10) led us to postulate that embryonic somatomedin production was regulated by substrates (11).

In further contrast to the adult where available evidence points to the liver as the major site of production (10), somatomedin may be produced by all fetal tissues. D'Ercole et al. (12) showed that immunoreactive SMC was produced by various fetal mouse explants. Preliminary studies in this laboratory using human fetal tissues confirm these findings. Such evidence points to the endogenous production of embryonic somatomedin which must then have a local paracrine action to regulate fetal cellular growth.

Acknowledgements

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