European Journal of Pharmacology, 106 (1985) 213–214
Elsevier

Rapid communication

NOVEL OPIOID PEPTIDES DERIVED FROM HUMAN β-CASEIN: HUMAN β-CASOMORPHINS

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Received 13 September 1984, accepted 13 September 1984

The β-casomorphins are a family of exogenous opioid peptides originally isolated from bovine casein peptone and comprising fragments of bovine β-casein (for review see Brantl and Teschemacher, 1983). Very recently it proved possible to elucidate the structure of human β-casein which differed from that of its counterpart, bovine β-casein in its primary structure (Greenberg et al., 1984). Interestingly such a difference occurred within the sequence equivalent to bovine β-casomorphins. Thus, the structure of bovine β-casein-(60-66) (Tyr-Pro-Phe-Pro-Gly-Pro-Ile or β-casomorphin-7) corresponds to that of human β-casein-(51-57) (Tyr-Pro-Phe-Val-Glu-Pro-Ile). The differences occur in positions 4 and 5 which are of major importance for the opioid activity of bovine β-casomorphins: β-casomorphin-4 and (-5) are the most potent representatives of the β-casomorphin family (Lottspeich et al., 1980). Therefore the equivalent (herein termed) 'human β-casomorphin-4 and (-5)' (Tyr-Pro-Phe-Val/Tyr-Pro-Phe-Val-Glu) were synthesized and their possible opioid potency evaluated.

Bovine and human β-casomorphin-4 and (-5) were synthesized by us according to the method previously described (Lottspeich et al., 1980) or purchased from Novabiochem, CH-4448 Läufelfingen, Switzerland. Peptides were tested for opioid activity in the electrically stimulated myenteric plexus/longitudinal muscle preparation of the guinea-pig ileum, GPI (Schulz and Goldstein, 1972).

Table 1 shows that the human β-casomorphins are less potent than the bovine β-casomorphins in the GPI bioassay (i.e. their IC_{50} values are higher).

Thus, it appears that human β-casein contains active opioid peptide sequences, as does bovine β-casein. Although their physiological significance is, as yet, incompletely defined, studies of ingested bovine β-casomorphins demonstrate that they exert a major influence upon endocrine secretion of, e.g., the pancreas (Schusdziarra et al., 1983). Evidently it is of clinical interest to determine whether the human β-casomorphins (-4) and (-5) or their larger fragments (-6) to (-8) could be formed in the organism upon ingestion of human milk and if such peptides could also modulate endocrine secretion.

TABLE 1

Opioid activities of bovine and human β-casomorphins in comparison to normorphine; values indicate concentrations (μM) causing 50% inhibition (IC_{50}) of electrically induced contractions of the guinea-pig ileum myenteric plexus/longitudinal muscle preparation (GPI); mean values from 4 determinations, standard deviations were less than 12% of mean values. Inhibitions of GPI were both reversed and prevented by the specific opioid antagonist naloxone (0.5 μM).

Substance		GPI
β-Casomorphin-4	(Tyr-Pro-Phe-Pro)	14.3
hβ-Casomorphin-4	(Tyr-Pro-Phe-Val)	56.2
β-Casomorphin-5	(Tyr-Pro-Phe-Pro-Gly)	2.0
hβ-Casomorphin-5	(Tyr-Pro-Phe-Val-Glu)	33.1
Normorphine		0.1

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