CELL PROLIFERATION IN THE INTESTINAL EPITHELIUM

A THESIS SUBMITTED FOR THE DEGREE OF
DOCTOR OF MEDICINE

by

BRIAN DESMOND CALLAGHAN,
MB., BS., F.R.A.C.S.,
F.R.C.S., F.R.C.S.E..

Department of Anatomy and Histology,
The University of Adelaide,
Adelaide,
South Australia.

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Previous investigators have suggested that the control of proliferative activity in the crypts of Lieberkühn of the small intestine is probably multifactorial and may include local mechanisms, direct and indirect effects of food in the lumen of the bowel, and systemic factors including humoral blood-borne factors, and effects mediated via the nervous system.

The main aim of the present study, using male Sprague-Dawley rats as experimental animals, was to use principally surgical experimental techniques to assess the influence of lesions of selected portions of the central nervous system (limbic system, pineal), and pertinent portions of the peripheral nervous system (vagus nerves, sympathetic nervous system), and combinations of these two, as well as certain other procedures judged to be appropriate to determine the mechanisms which control proliferative activity in the crypt cells, especially in relation to the nervous system and its particular role.

A total of 262 rats in 16 experimental procedures were used and the Colchicine stathmokinetic technique was used in all cases.

Bilateral cingulate or other neocortical lesions were not associated with any significant changes in crypt cell birth rate. On the other hand bilateral lesions of portions of the limbic system, viz., septum, fornix, hippocampus or amygdala, were associated with a rise in crypt cell birth rate of a considerable magnitude comparable with that following pinealectomy and unaffected by combinations of these lesions with pinealectomy. These results derived from the present study are consistent with the hypothesis that the effects of the
pineal on the gut are mediated via the limbic system, rather than the limbic effects being mediated via the pineal. The effects of limbic lesions on crypt cell proliferation rate have not been previously investigated, as far as can be determined from the available literature. The effects of pinealectomy are in accord with those of other workers using rats.

The effects of hippocampal lesions on the crypts appeared to be mediated in part by the autonomic nervous system, since they were diminished markedly by both vagotomy or local small intestinal denervation. Since the hippocampus is closely connected with the other parts of the limbic system, there is good reason to suspect that the effects of the lesions of other areas of the limbic system may also be mediated in a similar fashion. There does not appear to be evidence of such an investigation in the available literature.

Following pinealectomy there was a dramatic rise in the crypt cell birth rate. However, a finding of special interest is that crypt cell proliferation was found to be diminished below the expected level when pinealectomy was combined with, (i) truncal abdominal vagotomy, (ii) local small bowel denervation, but not by diversion of (iii) bile or (iv) luminal contents away from the intestinal epithelium. The findings regarding the effects of pinealectomy confirm those of other workers, but the effects of combining pinealectomy with the above mentioned changes have not been previously investigated, as far as can be determined from the available literature.

With regard to the functional implications of the above mentioned findings, the present investigator suggests that the pineal gland and the limbic system clearly appear to play some role in the general systemic modulation of crypt cell proliferation and exert such influence principally (although
probably not exclusively) via the autonomic nervous system. Further, it is still unclear whether the pineal gland and the limbic system are involved in day-to-day normal control mechanisms or act only under unusual conditions (e.g. stress).

Bilateral truncal abdominal vagotomy was found to be associated with a rise in crypt cell proliferation rate, in accordance with some workers but not others, since there is considerable difference of opinion in the literature on the effects of vagotomy on the crypts. However, stimulation of the abdominal vagus nerves was not associated with any significant change in the crypt cell proliferation rate, and this effect does not appear to have been previously investigated. With regard to the effects of vagotomy in association with pinealectomy or limbic lesions, it is notable that the effect of vagotomy on the crypts is to decrease the mitotic rate, suggesting that the vagus nerves have a different role when associated with such lesions.

Local denervation of loops of small intestine (mainly involving the sympathetic nerve supply) was associated with a significant fall in crypt cell proliferation rate which persisted for several weeks. Such effect was shown to be principally a direct neural one on the crypts, rather than being due to the local bowel ischaemia which may accompany this procedure. These findings are in accord with those of previous investigators, although the attempt to dissociate the neural from the local vascular effects does not appear to have been made by previous investigators.

Hyperphagia induced by dietary training was associated with a much smaller rise in crypt cell birth rate than that associated with limbic or pineal lesions, and neither pineal-
-ectomy nor limbic lesions were found to be associated with increased ingestion of food. In fact, there was not generally found to be any significant correlation between the amounts of food eaten and the rise or fall in crypt cell birth rate in the various experiments. The significance of this is discussed. There does not appear to have been an attempt to measure the amounts of food eaten in relation to the crypt cell mitotic rate made, on consulting the available literature.

This study has been made in an attempt to extend the amount of knowledge available about the topic of crypt cell proliferation control, especially in relation to the role of the C.N.S. in any such control mechanism, but obviously many questions remain unanswered as the mechanism of control of crypt cell proliferation is obviously a very complex one.