Serotonin as a Differentiation Signal

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The classic paper discussed in this essay:

► Lauder JM, Krebs H: Serotonin as a differentiation signal in early neurogenesis.
Dev Neurosci 1978;1:15–30.

We undertook this study [1] because we had found that serotonin (5-HT) as well as norepinephrine and dopamine neurons were born several days prior to those cells they will eventually innervate [2]. We chose to pharmacologically manipulate the developing serotonergic system in the embryo because of the availability of a drug, *p*-chlorophenylalanine (*p*CPA) that biochemically inhibited 5-HT synthesis [3], rather than destroying nerve terminals, as with 6-OH-dopamine [4].

This paper was highly cited because it provided the first evidence that 5-HT regulates differentiation of its target cells in the developing brain. This was based on the finding that treatment of pregnant rats with *p*CPA beginning on embryonic day 8, delayed the onset of differentiation (day of last precursor cell division) of neurons innervated by 5-HT nerve terminals in the adult brain (5-HT target cells) [1]. However, it was not known whether embryonic target cells of developing 5-HT neurons were similarly affected.

Following mapping of the prenatal development of the serotonergic system [5], we were able to examine the relationship of developing 5-HT nerve terminals to their embryonic target cells and reassess data from our previous *p*CPA study [6]. This analysis, together with a subsequent study [7], showed a strong correlation between the spatiotemporal distribution of developing 5-HT axons, inhibition of 5-HT synthesis within these cells [7], and delayed onset of neuronal differentiation in specific regions of the embryonic rat brain [6].

Since this time, many studies have provided evidence that 5-HT acts as an important differentiation and growth regulatory signal that plays key roles in the development of the nervous system [8] as well as nonneural tissues [9]. These roles are mediated by the same receptors and second messengers utilized in neurotransmission [10], but in developing tissues, including the CNS [11, 12], gut, heart and craniofacial region [9, 13–18], ongoing ontogenetic processes allow these signals to act like growth, trophic and morphogenetic signals.

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