

# Two kinds of tryptamine receptor

J.H. Gaddum & Z.P. Picarelli

*Commentary by*

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As John Donne so perceptively observed, "no man is an island". So it is in science where it is rare indeed to find even a profoundly significant development which did not rely substantially on the insight and experimental efforts of others. The paper of Gaddum and Picarelli, although unquestionably seminal, is an excellent example of Donne's aphorism in that the core experimental data were essentially confirmatory. Thus, as clearly and generously conceded in the paper itself, the neuronal locus for 5-HT in contracting the guinea-pig ileum and the effects of atropine, morphine and cocaine had been previously described by others. Moreover, even the momentous conclusion had been anticipated some four years previously by Gaddum himself who wrote (Gaddum and Hameed, 1954) "...there are two types of tryptamine receptor. One type is present in the smooth muscle of the uterus and ear and is specifically inhibited at low concentrations of lysergic acid diethylamide (LSD). The second type is present in the nervous tissues in the ileum and is not inhibited by LSD".

What then made "Gaddum and Picarelli" so significant? I believe two factors were important. First, the initiative to name the receptors drove home unequivocally the message of the plurality of receptors for 5-HT and provided the first "classification" of the sites. Second, and paradoxically, almost from the moment of its appearance the classification was widely and repeatedly criticized largely on the basis of the use of morphine and dibenzylamine, the drugs giving rise to the M and D nomenclature. Truly, there is no such thing as bad publicity!

The key messages of "Gaddum and Picarelli" are clearly set out in the first and last sentences of the admirably concise summary. The first, suitably authoritative, states "There are two kinds of tryptamine receptor in the guinea-pig ileum, namely the M receptors which can be blocked with morphine

and the D receptors which can be blocked by dibenzylamine". The second, appropriately circumspect, reads, "The M receptors are probably in the nervous tissue and the D receptors are probably in the muscles". These conclusions were based on the quite distinct pharmacology of the contractile responses of the guinea-pig ileum to 5-HT when the tissue was incubated with either morphine (1 µg/ml) or dibenzylamine (0.1 µg/ml). A series of preliminary experiments was carried out to define the validity of these conditions; the definitive pharmacology was carried out with the tissue set up in either the M or D receptor modes. It bears emphasis that, unlike the majority of previous investigations in this field, Gaddum and Picarelli's findings were based on quantitative analyses which defined the effects of the blocking drugs by dose-ratio measurements and the all important selectivity by monitoring the effects of the antagonists on contractile responses to histamine and nicotine. The observation that the "antagonism ... [of atropine] ... to the action of nicotine is comparatively feeble" induced Gaddum and Picarelli to keep an open mind as to the precise location of the M receptor thereby anticipating the increased complexity of the interaction of 5-HT (and indeed nicotine) with the nervous elements of the ileum destined subsequently to be unravelled by others.

Of course, with hindsight, morphine and dibenzylamine were clearly inappropriate tools for receptor classification. Indeed, Gaddum and Picarelli themselves were under no illusion as to the deficiencies in the use of morphine. In the final sentence of their paper they acknowledge that, there is "no proof that... [5-HT and morphine]...act on the same receptors as one another". But there has been a tendency to overlook the fact that Gaddum and Picarelli substantiated their results with dibenzylamine using LSD, dihydroergotamine and bromolysergide. Moreover, in addition to morphine, they used cocaine which also gave selective blockade

of the response to 5-HT mediated through the M receptor. Importantly, after almost 40 years, the basic concept that the guinea-pig ileum contains at least two distinct 5-HT receptors, one on the smooth muscle cells and a second associated with the intramural nervous tissue remains entirely valid.

It is now clear that at least 15 gene products can be classified at 5-HT receptors and that the major-

ity of these are present in the guinea-pig ileum. Such diversity is recognized by continual revision of increasingly complex 5-HT receptor classification schemas. Of course, Gaddum and Picarelli's nomenclature has long been abandoned; the sites, however, remain as fully accepted members of the 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptor categories, striking testimony to the essential correctness of the M and D classification.

## References

- GADDUM, J.H. & HAMEED, K.A. (1954). Drugs which antagonise 5-hydroxy tryptamine. *Br. J. Pharmacol.*, **9**, 240-248