Reply: cannabinoid paths to anti-diarrheal drugs

We are delighted at this opportunity to discuss an important facet of the endogenous cannabinoid system, which we had overlooked more for the sake of space than for lack of interest. We agree with Capasso and his colleagues that the presence of cannabinoid receptors in the gastrointestinal tract is of considerable physiological and pharmacological relevance. As these authors point out, a substantial body of evidence indicates that cannabinoid drugs inhibit intestinal motility in rodents, presumably through modulation of neurotransmitter release in the enteric nervous system[1–3]. The fact that marijuana smokers do not typically cite constipation among the most prominent effects of this drug (as do opium users) is disappointing, but it might simply reflect the need for more thorough clinical tests.

If cannabis-derived drugs were found to inhibit gut motility in humans, the main obstacle to the therapeutic use of these compounds for intestinal disorders would be represented by their psychotropic or cardiovascular actions. Thus, the question that needs to be addressed is whether drugs that act on the cannabinoid system can achieve a significant degree of control of intestinal motility without provoking unacceptable systemic side-effects. In this regard, two possible approaches might be explored. The first is to develop cannabinoid receptor agonists that have restricted access to the CNS. This goal could be achieved, following the model of the anti-diarrheal opiate loperamide (Imodium®)[4], by designing cannabinoid compounds that are incompletely absorbed following oral administration. The second approach could be to develop inhibitors of endocannabinoid transport and/or enzymatic degradation – a family of pharmacological agents that might have greater pharmacological selectivity than direct-acting cannabinoid drugs[5]. However, to validate such approaches we need to learn more about the functional roles of the endocannabinoid system in the gut, which are still largely unknown. Are the endocannabinoids anandamide and 2-arachidonylglycerol (2-AG) released by cells in the gastro-intestinal tract and, if so, under what circumstances? Do these compounds participate in the normal or pathological regulation of gastrointestinal function and, if so, in which specific ways? How are anandamide and 2-AG deactivated in the gut? Answering these questions is essential to define the specific components of the intestinal endocannabinoid system that might serve as targets for therapeutic drugs.

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Astrocyte–neurone crosstalk: variants of the same language?

In a *TiPS* recent article[1], Gallo and Ghiani review much of the most recent data on the expression of different glutamate receptors in glial cells. In addition, the authors provide an excellent survey of the current understanding of the regulation and function of these receptors in glia. By summarizing the available data on glutamate-receptor-mediated neurone–glia interactions, the authors emphasize the emerging view that a close bidirectional communication between neurones and astrocytes might exist in the brain and that this is mediated by the same agent – the excitatory amino acid glutamate. Indeed, it is now firmly established that glutamate released from synaptic terminals can activate ionotropic and metabotropic glutamate receptors on astrocytes, triggering elevations in the intracellular concentration of Ca^{2+} $\{[Ca^{2+}]_i\}$ in these cells[2–4]. But astrocytes can also talk back to neurones by releasing glutamate, which acts on glutamate receptors on neurones[4,5]. The activation of glutamate receptors results in elevations in $[Ca^{2+}]_i$ that might exert multiple actions on neuronal function. Indeed, the authors highlight the recent evidence obtained from both neurone–astrocytes co-cultures and acute brain-slice preparations for the involvement of glutamate release from astrocytes in the modulation of neuronal excitability and synaptic transmission.

Astrocytes are accurate sensors of neuronal activity

I should like to discuss a few aspects of the reciprocal signalling between neurones and astrocytes, including the possible rules governing these interactions, which were not addressed in depth in the Gallo and Ghiani review. It is worth underlining that although we would not expect this form of bidirectional signalling to represent a mode of information transfer as rapid as neuronal synaptic transmission, it is certainly possible that it does carry some relevant pieces of information. This raises several questions. Under what conditions can the glutamate released from synaptic

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