Metabolic recruitment of spinal locomotion: intracellular neuromodulation by trace amines and their receptors

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**PERSPECTIVE**

**Metabolic recruitment of spinal locomotion: intracellular neuromodulation by trace amines and their receptors**

The trace amines (TAs) are a family of endogenous amines with structural, metabolic, physiological and pharmacological similarities to classical monoamine neurotransmitters. The TA family includes tyramine, octopamine, β-phenylethylamine (PEA), and tryptamine (Figure 1). Their presence has been well documented in all vertebrate and invertebrate species studied. Like the classical monoamines, the TAs are synthesized via enzymatic decarboxylation of the precursor aromatic amino acids phenylalanine, tyrosine, and tryptophan with aromatic L-amino acid decarboxylase (AADC; also called DOPA decarboxylase). For decades, researchers have known that these amines are present in the brain. A large earlier literature asserted their role as endogenous neuromodulators of monoaminergic excitability and neurotransmission, challenging the more conventional view that was indistinguishable from that ordinarily observed with serotonin (5-HT). This suggested actions on common central pattern generating neurons (Figure 2A). The TAs also generated distinctive complex rhythms characterized by episodic bouts of locomotor-like activity that supported recruitment of additional circuits (Figure 2B). TA actions on locomotor circuits did not require interaction with descending monoaminergic projections since evoked motor rhythms were maintained following block of all Na*-dependent monoamine transporters or the vesicular monoamine transporter. Instead, TA (tryptamine and tyramine) actions depended on intracellular uptake via pentamidine-sensitive Na*-independent membrane transporters. Requirement for intracellular transport was consistent with the TAs having much slower locomotor onset than 5-HT and for activation of intracellular TAARs. Behaviorally, the actions of applied TAs integrated well with their known pharmacological sympathomimetic function. To test for endogenous actions following biosynthesis, we increased intracellular amino acid levels with cycloheximide. Locomotor-like activity emerged and included distinctive TA-like episodic bouts. Putative cellular transport mechanisms are outlined in Figure 2C. Overall, both our anatomical and functional evidence supported a role of the TAs as an intrinsic spinal monoaminergic modulatory system that was capable of promoting recruitment of locomotor circuits independent of the descending monoamines. Provided evidence of a spinal cord substrate for TAs with independent intrinsic biological actions supported the TAs as bona fide endogenous monoamines neuromodulators with their own unique neuromodulatory status.

**Possible functional roles of trace amine signaling:** Intracellular transport appears to be a prominent requirement for observed TA actions, and this suggests that intracellularly synthesized TAs may act to intrinsically modulate their own function independent of external neuronal interactions. This occurs presumably via TAAR-mediated changes in signal transduction pathways that modulate cellular/synaptic activity (Figure 2C). If intracellular TA biosynthesis was regulated by subcellular substrate precursor amino acid availability for subsequent intracellular TAAR activation, increases in activity may follow activation of amino acid mobilizing catabolic pathways. In this way intracellularly-synthesized TAs may comprise an integral cellular metabolic cascade for temporary augmentation of motor activity. For example, such a cascade could be a component part of an innate multi-organ system autonomic sympathetic stress response (e.g., fight or flight). This is consistent with TAARs being important olfactory odorant receptors in innate survival responses (Liberles, 2015). It is also consistent with observed sympathomimetic cardiovascular actions (Broadley, 2010).
Figure 1 Comparison of monoamine synthesis pathways.

(A) The trace amines (TAs) are a group of endogenous monoamines that include tryptamine, tyramine, octopamine and β-phenylethylamine (PEA; blue). The TAs have structural, metabolic, physiologic, and pharmacologic similarities to the classical monoamine transmitters (green) and are synthesized from the same precursor aromatic amino acids (red). Unlike the classical monoamines, aromatic-L-amino acid decarboxylase (AADC; also called dopa decarboxylase) is the only enzyme required to produce them. Conversion from the TAs to the monoamines does not appear to occur. (B) Overview showing that, like the classical monoamine transmitters, the TAs are degraded by the monoamine oxidases.

this context, intrinsic TA facilitation of the locomotor system may arise from phylogenetically primitive innate locomotor escape responses that reside completely within the spinal cord. Metabolic mechanisms that promote response amplification would clearly be adaptive in survival responses.

The previously described high TA synthesis rates may provide an additional important clue to their function. High synthesis rates support rapidly adjustable shifts in TA levels that are exquisitely attuned to moment-to-moment fluctuations in bioavailable precursor amino acid substrate availability. Alternatively, assuming full substrate availability, signal transduction-mediated alterations in AADC activity could serve to adjust endogenous TA levels and act as a variable gain modulator of circuit function. This would apply anywhere there was TAAR1 and/or TAAR4 expression in AADC+ neurons. Moreover, if the TAs are bi-directionally transported across membranes by widely expressed transporters (Figure 2C), neurons expressing TAAR1 and/or TAAR4 could be modulated by nearby AADC+ TA-producing cells. As AADC is expressed in spinal cord vasculature (Gozal et al., 2014; Li et al., 2014) and expression in microvasculature is strongly modifiable (Li et al., 2014), the circulatory system may afford diffuse TA delivery for broad TA-based modulation.

Proposed future studies: Future studies are required to validate and extend our initial findings and would be aided with transgenic approaches and the use of selective TAAR agonists and antagonists. One immediate question is whether the TAs integrate and interact with conventional monoamines to modulate the locomotor system. The answer is yes, as we have observed that TA actions are broadly facilitatory to ongoing 5-HT-induced locomotion (Gozal and Hochman; unpublished observations). Experimental support for modulatory actions of the TAs on motor behavior in adult preparations would importantly extend our observations in neonates. Perhaps most essential is to undertake experiments that mechanistically link the chain of hypothesized endogenous events. This includes; (i) identification of the physiological trigger that increases bioavailable aromatic amino acids, (ii) subsequently increasing endogenous TA synthesis levels, (iii) activating TAARs, and (iv) facilitating locomotor activity. A conceptual framework related to mechanisms of cellular stress may be a good starting point for such studies.

Possible neurotherapeutic interventions: As the TA/TAAR modulatory system may help set the baseline excitability of spinal motor systems, therapeutic elevations or reductions in TAAR signaling may help control aberrant motor excitability in various disease states. For example, it may turn out that the TA/TAAR modulatory system is better at temporal motor gain control than the classical monoamines.

Unfortunately, while mechanisms that selectively alter endogenous TA levels may have neurotherapeutic relevance, their synthesis and degradative enzymes are common to the classical monoamines. Thus, elevating expression levels via block of degradation (e.g., MAO inhibitors) would also alter classical monoamine content and actions. However, selective signal transduction-mediated alterations in AADC activity could selective have more preferential impact on the TAs (Berry, 2004). Alternately, if substrate availability is rate-limiting for TA biosynthesis (e.g., but not for the classical monoamines with vesicle pool reserves), simply increasing substrate availability with dietary precursor amino acid supplementation, or providing TAs directly (e.g., elevated in chocolate, aged cheeses, and wines) could have functional consequences on motor circuits of neurotherapeutic relevance (Jackson, 1975).

Classical monoamine receptor agonists improve locomotor functional outcome after SCI in animal models (Courtine et al., 2009). We demonstrate that the TAs act as an intrinsic spinal cord monoaminergic modulatory system. They recruit locomotor patterns that include unique episodic events not activated by the classical monoamines (Gozal et al., 2014). This, and our unpublished observations that they facilitate ongoing 5-HT-induced locomotion, supports consideration of TAs or TAAR receptor activation in the management of SCI with compromised descending monoaminergic systems. For example, strategically-timed delivery of aromatic amino acid precursors and/or TA dietary supplements for SCI patients could improve motor performance, including motor endurance by their cardiovascular
A2) Episodic bouts of locomotor-like rhythms seen with the descending neuromodulatory transmitter 5-HT. (B) TA-induced slower activity rhythms onto neurons that drive the CPG could lead to the episodic waxing and waning of rhythmic output to motor neurons. Candidate neurons are the lamina X AADC are shown for tyramine and waveform at right. (B) Proposed circuit locations for TA-induced modulatory actions in the emergence of continuous and episodic locomotor port into neurons via Na+-independent membrane transporters allows for trace amine-associated receptors (TAAR)-containing neurons to also be modulated by TA following their exogenous application, (ii) release from AADC expressing neurons (iii) here neuron I onto neuron II or (iii) release from AADC-expressing endothelia.

Figure 2 Example activity patterns (A), hypothetical network (B) and cellular pathways (C) for trace amine-mediated actions. (A1) Examples of continuous locomotor rhythms generated in the presence of 5-hydroxytryptamine (5-HT) and the trace amines (TAs). Shown are smoothed activity pattern envelopes reporting activity for right (blue) and left flexors (red), (A2) Episodic bouts of locomotor-like rhythms are shown for tyramine and β-phenylethylamine (PEA) at slow (left) and expanded time scales (right). Bar over epochs at left identified expanded waveform at right. (B1) TA modulatory actions intrinsic to locomotor central pattern generating neurons (CPG) would produce actions comparable to those seen with the descending neuromodulatory transmitter 5-HT. (B2) TA-induced slower activity rhythms onto neurons that drive the CPG could lead to the episodic waxing and waning of rhythmic output to motor neurons. Candidate neurons are the lamina X AADC D cells. (C) Putative transport and intracellular signaling mechanisms for observed TA actions. The TAs are synthesized from their precursor aromatic amino acids (AAAs) via the essential synthesis enzyme AADC. Intracellular TAs act on TAARs to produce G protein-coupled neuromodulatory responses. TA transport into neurons via Na+-independent membrane transporters allows for trace amine-associated receptors (TAAR)-containing neurons to also be modulated by TA following their exogenous application, (ii) release from AADC expressing neurons (iii) here neuron I onto neuron II or (iii) release from AADC-expressing endothelia.

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References