

## Opposing actions of 5HT<sub>1A</sub> and 5HT<sub>2</sub>-like serotonin receptors on modulations of the electric signal waveform in the electric fish *Brachyhypopomus pinnicaudatus*

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### Abstract

Serotonin (5-HT) is an indirect modulator of the electric organ discharge (EOD) in the weakly electric gymnotiform fish, *Brachyhypopomus pinnicaudatus*. Injections of 5-HT enhance EOD waveform “masculinity”, increasing both waveform amplitude and the duration of the second phase. This study investigated the pharmacological identity of 5-HT receptors that regulate the electric waveform and their effects on EOD amplitude and duration. We present evidence that two sets of serotonin receptors modulate the EOD in opposite directions. We found that the 5HT<sub>1A</sub>R agonist 8-OH-DPAT diminishes EOD duration and amplitude while the 5HT<sub>1A</sub>R antagonist WAY100635 increases these parameters. In contrast, the 5HT<sub>2</sub>R agonist  $\alpha$ -Me-5-HT increases EOD amplitude but not duration, yet 5-HT-induced increases in EOD duration can be inhibited by blocking 5HT<sub>2A/2C</sub>-like receptors with ketanserin. These results show that 5-HT exerts bi-directional control of EOD modulations in *B. pinnicaudatus* via action at receptors similar to mammalian 5HT<sub>1A</sub> and 5HT<sub>2</sub> receptors. The discordant amplitude and duration response suggests separate mechanisms for modulating these waveform parameters.

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Serotonin (5-HT) is a neuromodulator so ubiquitous that hardly any physiological function or behavior is free from its direct or indirect effects. As a result, a full account of neuroendocrine control of behavior requires a thorough assessment of 5-HT's function across a wide range of circumstances, even as the pervasive presence of 5-HT in the nervous system complicates unambiguous assessment of its functions. Particularly, serotonin is involved in the regulation of diametrically opposed behaviors, aggression and subordination (Summers and Winberg, 2006). Serotonin activity rises in both dominant and subordinate males but rapidly returns to baseline in dominants while it stays chronically high in subordinates (Overli et al., 1999; Summers and Winberg, 2006). Prior social defeat or success during aggressive interactions affects future aggressive behaviors and the activity of the serotonergic system (Winberg

et al., 1992; Winberg et al., 1997b). Furthermore, social experience affects the regulatory effect of serotonin on dominant behaviors via serotonin receptors 1A and 2A (Yeh et al., 1996).

Pharmaceutical 5HT<sub>1A</sub> agonists inhibit aggression or induce submissive behaviors in a wide range of non-mammalian vertebrates including green anoles (Deckel and Fuqua, 1998), Arctic charr (Hoglund et al., 2002; Winberg and Nilsson, 1993), rainbow trout (Winberg et al., 1997a), and sticklebacks (Bell et al., 2007). In addition, 5HT<sub>1A</sub> receptors operate as both post-synaptic receptors and as pre-synaptic autoreceptors to either suppress or stimulate stress responses in teleosts as they do in mammals (Hoglund et al., 2002). Despite the functionally and anatomically conserved nature of the serotonin system in vertebrates (Parent et al., 1984) and the abundance of data indicating a role for 5HT<sub>1A</sub> receptors in regulating social behaviors in fish, nothing is known about the function of 5HT<sub>2</sub>-like receptors in teleosts (Bagdy, 1996; Eison and Mullins, 1996). The complexity of the 5-HT receptor system and the multiple levels upon which serotonin influences physiology and

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behavior hints at a system capable of producing contextually appropriate responses to a wide range of stimuli using the same structures, circuits, and ligands.

Gymnotiform fish are excellent models to evaluate the processes underlying the connection between environmental stimuli, motivational state and behavioral output. These fish emit an easily-quantifiable electric signal generated by a well-mapped neural motor network. Male–male interactions alter these electric signals. Furthermore, the electrocommunication network of these fish is dynamic, and is modulated by hormones, modulators, and neurotransmitters. Thus, changes in the electric signal of males during aggressive interactions give us a real-time broadcast of the neuromodulatory regulation of the electrocommunication signals of competing males.

The electric organ discharge (EOD) of weakly electric gymnotiform fish is a dual-purpose signal used to navigate and communicate in total darkness. The EOD pulse of *Brachyhypopomus pinnicaudatus* is a biphasic sinusoidal wave that increases or decreases in amplitude and in the duration of the second phase (Fig. 1). The EOD is produced by electrocytes — specialized excitable cells in the peripheral electric organ. Social encounters and environmental stimuli modulate the EOD waveform by altering the membrane biophysics and discharge waveforms of individual electrocytes (Ferrari et al., 1995; McAnelly and Zakon, 2000; Mills and Zakon, 1991), resulting in either a larger or smaller waveform. Social encounters modulate the EOD within minutes and large waveforms and/or rapid enhancements are associated with dominance status (Franchina et al., 2001; Hagedorn and Zelick, 1989; Stoddard et al., 2003).

We have shown that intramuscular injections of 5-HT cause male *B. pinnicaudatus* to increase their EOD amplitude and duration akin to the waveform changes observed during male–male social interactions (Stoddard et al., 2003). These effects of 5-HT do not result from its direct action on the electrocytes, whereas melanocortin peptides do modulate the discharge waveforms of single electrocytes directly (Markham and Stoddard, 2005). Thus, it is possible that 5-HT modulates EOD waveform by acting centrally to elicit release of melanocortins into circulation.

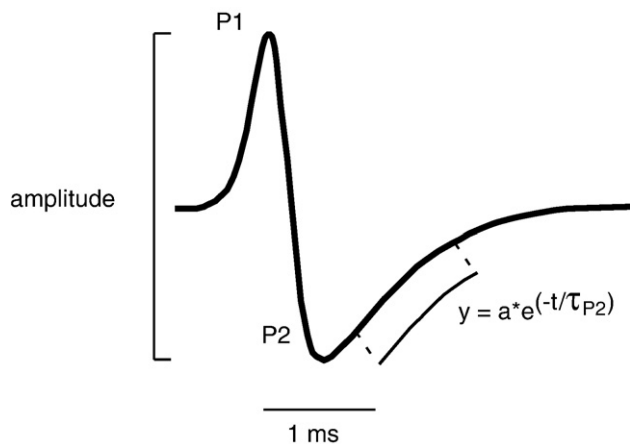


Fig. 1. Measure of *Brachyhypopomus pinnicaudatus* EOD waveform parameters. Amplitude was measured peak-to-peak for the whole waveform. The time constant of repolarization of the 2nd phase,  $\tau_{P2}$ , was estimated by fitting an inverse exponential function to the decay segment.

Therefore we sought to clarify the proximate mechanisms of serotonin's action on EOD modulations in *B. pinnicaudatus*.

The 5-HT system consists of extensive projections of serotonergic neurons throughout the brain and a labyrinthine system of serotonin receptors. Seven distinct 5-HT receptor families (5HT<sub>1R</sub>–5HT<sub>7R</sub>) have been identified and some families possess multiple receptor subtypes (e.g., 5HT<sub>2A</sub>, 2B, 2C) (Glennon et al., 2000). Stimulating (or blocking) different serotonin receptor types often results in opposite actions on target tissues (Welch et al., 1993). The seemingly incongruous role of the same agonist as activator and inhibitor can be explained by evidence that different serotonin receptor types activate different serotonergic signaling pathways, each of which produces different results downstream (Jorgensen et al., 1998; Saphier et al., 1995; Welch et al., 1993). Studies have confirmed that 5-HT receptors with pharmacological profiles similar to mammalian 5HT<sub>1</sub> and 5HT<sub>2</sub>-like receptors are present in teleosts, and at least three different 5-HT receptor types have been localized in whole teleost brain homogenates (Dietl and Palacios, 1988; McDonald and Walsh, 2004; Winberg and Nilsson, 1996; Yamaguchi and Brenner, 1997).

Our objective in this study was to clarify our understanding of serotonergic regulation of weakly electric social signals and to identify which 5-HT receptor types were pharmacologically linked to changes in EOD. We used various serotonergic compounds to assess activity and directionality of EOD modulations in response to activating or inhibiting specific 5-HT receptor types. We found that the opposing actions of two serotonin receptors showing pharmacology characteristic of the mammalian 5HT<sub>1A</sub>R and 5HT<sub>2R</sub> regulate the EOD waveform.

## Methods

### Animals

Sexually mature male *B. pinnicaudatus* (Hopkins, 1991), bred and maintained on Florida International University campus, were randomly collected from outdoor breeding pools throughout 2002–2006 and brought indoors for pharmacological challenge tests ( $n=4-12$  males per trial). Fish were weighed and measured prior to placement in separate recording tanks to calculate appropriate injection doses and then left undisturbed for a minimum of 24-h before pharmacological challenges were administered to allow individuals to acclimate to their tanks and to measure baseline EODs.

All methods used in these experiments were approved in advance by the FIU IACUC and complied with the "Principles of Animal Care" publication No. 86-23, revised 1985, of the National Institutes of Health.

### Electric signal recording

We recorded EODs with an automated, calibrated recording system previously described in detail (Stoddard et al., 2003). The system automatically records EODs when the fish passes through or rests in the geometric center of the tank. EODs are collected approximately once a minute around the clock throughout the duration of each experiment. We measured amplitude of the EOD waveform peak-to-peak, and duration of the second phase as  $\tau_{P2}$ , the time constant of an inverse exponential function fit to the decay segment of the second phase (P2) of the EOD waveform (Fig. 1).

### Chemicals and reagents

Table 1 shows reported mammalian 5-HT receptor affinities of the serotonergic drugs that we used to characterize the mechanisms of 5-HT activity.

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