Review Article

Neuropharmacology of the mesolimbic system and associated circuits on social hierarchies

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Abstract

Most socially living species are organized hierarchically, primarily based on individual differences in social dominance. Dominant individuals typically gain privileged access to important resources, such as food, mating partners and territories, whereas submissive conspecifics are often devoid of such benefits. The benefits associated with a high social status provide a strong incentive to become dominant. Importantly, motivational- and reward-related processes are regulated, to a large extent, by the mesolimbic system. Consequently, several studies point to a key role for the mesolimbic system in social hierarchy formation. This review summarizes the growing body of literature that implicates the mesolimbic system, and associated neural circuits, on social hierarchies. In particular, we discuss the neurochemical and pharmacological studies that have highlighted the contributions of the mesolimbic system and associated circuits including dopamine signaling through the D1 or D2 receptors, GABAergic neurotransmission, the androgen receptor system, and mitochondria and bioenergetics. Given that low social status has been linked to the emergence of anxiety- and depressive-like disorders, a greater understanding of the neurochemistry underlying social dominance could be of tremendous benefit for the development of pharmacological treatments to dysfunctions in social behaviors.

Keywords: *Dopamine; Dominance; Social Hierarchy; Mesolimbic system; Mitochondria; Nucleus Accumbens; Ventral Tegmental Area*

1. Introduction

Across species, ranging from invertebrates (Cole, 1981) to primates (Desjardins et al., 1973, Zhou et al., 2018), social groups naturally organize into hierarchies (Dunbar and Dunbar, 1977, Pusey et al., 1997, van Noordwijk and van Schaik, 1999). In general, dominant individuals achieve higher benefits across many life domains, such as the formation of effective alliances, the allocation of territory or privileged access to reproduction and other resources (Sapolsky, 2005). Importantly, the limited resources available for submissive individuals may have detrimental health consequences. In humans, it has been shown that individuals of lower social status suffer considerably from mental disorders such as anxiety and depression (Gilbert and Allan, 1998, Wilkinson, 1999), and exhibit increased rates of mortality as compared to individuals of higher social rank (Antonovsky, 1967, Syme and Berkman, 1976, Sapolsky, 2005). Thus, an in-depth understanding of the neural mechanisms underlying social dominance may be greatly beneficial to our health. In particular, advancing on the neuropharmacology of social hierarchy formation and maintenance can guide pharmacological approaches effective to treat dysfunctions in the social domain.

Various intrinsic traits such as sex, age and size, as well as extrinsic factors such as prior social experience or parental rank might regulate individuals' place in a social hierarchy (Chase et al., 2002, Borglum et al., 2003, Bartolomucci et al., 2005, Cordero and Sandi, 2007). Once established, social hierarchies tend to be stable over long periods of time (Broom, 2002). Hence, the outcome of an initial encounter between two or more individuals may have important lasting consequences (Cordero and Sandi, 2007, Timmer and Sandi, 2010).

Recent advances were made in identifying discrete brain regions that are important in mediating social rank, as well as the neurobiological underpinnings that take place at the molecular and cellular level. The reward- and motivation-related mesolimbic dopamine system is prominent among the identified neural circuits relevant for social dominance. In rodents, intact function of the nucleus accumbens (NAc) and accumbal dopaminergic inputs from the ventral tegmental area (VTA) are crucial for the outcome of a social competition (Hollis et al., 2015; van der Kooij et al. 2018a). Human imaging data has indicated increased ventral striatal

activation (which contains the NAc) when individuals are winners in a competitive setting (Zink et al., 2008). This focused review summarizes the growing evidence demonstrating the involvement of the mesolimbic system in the regulation of social dominance. Other, more general aspects of social dominance, such as the use of protocols for social hierarchy testing in rodents or the wider involvement of brain regions to the establishment or maintenance of social hierarchies haven been recently reviewed elsewhere (Qu et al. 2017; Zhou et al. 2018). Our focus on the mesolimbic system reflects the emerging importance of bioenergetics and mitochondrial functions of the mesolimbic system in social dominance. It is important to note that these mesolimbic and accumbal circuits exhibit bidirectional connections with other brain regions, such as the hippocampus, amygdala, and prefrontal cortex (Hyman et al., 2006, Arnsten et al., 2012, Russo and Nestler, 2013), that are involved in the processing and/or representation of social hierarchies (Rosvold et al., 1954, Timmer et al., 2011, Wang et al., 2011, Noonan et al., 2014, Watanabe and Yamamoto, 2015, Hollis et al., 2018).

2. The VTA-NAc circuitry in the regulation of social dominance

Accumulating evidence has coupled social dominance to motivation-driven processes. In mice, social motivation was linked to social dominance (Kunkel and Wang, 2018). Similarly, observations in the visible burrow system (VBS), a model in which rats form dominance hierarchies, showed that dominant rats display increased operant responding for a food reward relative to subordinates and controls (Davis et al., 2009). Interestingly, social submission appears to coincide with a reduction of motivational drive. Specifically, chronic social defeat stress in mice was shown to reduce reward-directed behavior in an operant conditioning task and to be associated with a reduction of dopamine turnover in the NAc (Bergamini et al. 2018). The VTA-NAc pathway is best known for its role in a broad range of motivation-related behaviors and in processing both rewarding and aversive events (Lammel et al., 2014, Pignatelli and Bonci, 2015, Schultz, 2016, Watabe-Uchida et al., 2017) and may thus be centrally involved in the neural regulation of social dominance.

Recent studies have identified the engagement and, to some extent, the causal implication of the VTA and the NAc in the expression of social dominance. In hamsters, increased number of cFOS-immunoreactive cells were

found in the VTA for those individuals that displayed higher social dominance behaviors (Gil et al., 2013). In humans, functional magnetic resonance (fMRI) imaging revealed an enhanced signal response of the ventral striatum when observing the face of a highly-ranked opponent, as compared to the face of a lower-ranked opponent (Zink et al., 2008). This activation was highest when participants were informed of their win or loss (Zink et al., 2008). These findings suggest that striatal activity in a competitive setting depend on intrinsic motivation as well as on the rank of the opponent. Several animal studies have also highlighted a commanding role for the NAc in the expression of social dominance. In rats, immunohistochemistry experiments showed that social competition increases cFOS activity in NAc neurons (Hollis et al., 2015). Conversely, temporary inactivation of the NAc through local microinfusion of the $GABA_A$ agonist muscimol reduces social competitiveness (Hollis et al., 2015). Altogether, these findings support a key role for the NAc in social dominance, adding to its known involvement in reward learning and motivational processes. While the studies suggest that activation of VTA-NAc pathway is essential for the regulation of social dominance, the involvement of reciprocal pathways in social dominance remains an open question.

3. The role of dopamine in the regulation of social dominance

Given that the VTA and NAc are heavily engaged upon social competition (see above) and that dopamine signaling is a core phenomenon within the mesolimbic system, it is not surprising mesolimbic dopamine itself emerges as a central element in the establishment of a social hierarchy. There is ample evidence for the involvement of mesolimbic dopamine in social dominance across taxa. In lizards, for example, enhanced dopamine concentrations in the VTA and NAc have been associated with higher dominance (Korzan et al., 2006). In crickets, dopamine is required to overcome the effects of social defeat and necessary for the subsequent re-expression of competitive behaviors (Rillich and Stevenson, 2014). The dopamine transporter (DAT), as main dopamine reuptake mechanism in the brain, is an important regulator for dopaminergic neurotransmission, and genetic studies suggest ist implication in social status. Thus, two single-nucleotide polymorphisms (SNPs) located in the 5' untranslated region of the DAT gene (SLC6A3) were linked to social

dominance in cynomolgus macaques (Miller-Butterworth et al., 2008). In rodents, optogenetic and neuropharmacological studies have revealed that phasic stimulation of dopamine firing triggers social avoidance and facilitates susceptibility to develop depression-like behaviors following exposure to chronic social defeat (Cao et al., 2010, Chaudhury et al., 2013).

In the mammalian brain, dense dopaminergic efferent projections from the VTA terminate into the NAc where medium spiny neurons (MSNs) contain dopamine D1- and/or D2 receptors (Francis and Lobo, 2017). The MSNs comprise the predominant neuronal population (about 95%) of the NAc. Projections from the accumbal MSNs to the ventral pallidum and midbrain include contributions from both D1- and D2 receptor-contaning neuronal populations. However, a clear-cut segregation of D1- and D2 receptor-containing MSNs into specific pathways, as typically described for MSNs from the dorsal striatum, has not been confirmed for NAc projections (Kupchik et al., 2015). Importantly, though, since D1/D2 receptor co-expressing neurons only comprise about 6% of the MSNs (Betran-Gonzalez et al. 2008), functional differences produced by divergent activation patterns of these specific MSNs subpopulations remain a possibility. Accordingly, distinct roles for D1- and D2-receptors have been recognized in several brain functions and behaviors including, for example, stress-induced depressive-like behaviors (reviewed in Francis and Lobo, 2017).

Concerning social dominance, a number of studies have aimed to investigate the contributions of the D1 and D2 receptors in the mesolimbic system and associated circuits. In hamsters, intra-accumbal infusion of a non-specific D1/D2 receptor antagonist, cis(z)flupenthixol, reduced the lack of competitive behavior induced by social defeat (Gray et al., 2015). In rats, social competition led to increased cFOS activation in D1-containing cells but not in D2-containing cells, astrocytes or cholinergic cells (Hollis et al. 2015). Critically, the extent of cFOS expression within these D1 receptor-containing cells correlated with the amount of offensive behavior expressed during social competition, while no such correlation was found for any of the other NAc cell types examined (Hollis et al. 2015). In another study, low anxious rats that tend to win a social competition against high anxious rats, expressed a higher number of cFOS-positive cells containing D1 receptors in the NAc, while

no group differences were found for the number of D2 receptor containing cFOS-positive cells (van der Kooij et al. 2018). Pharmacological studies have further supported a causal role for NAc D1 receptor activation in social dominance. In rats, infusion of a D1 receptor agonist (SKF-38393) in the NAc of one of two males submitted to a social competition encounter enhanced social dominance (van der Kooij et al. 2018a). However, a recent study in mice and non-human primates showed that systemic administration of a D1 receptor antagonist (SCH-23390) facilitated or did not modify, respectively, social competition (Yamaguchi et al., 2017a), which contrasts with the dominance-promoting role of the accumbal D1 receptor discussed above. These findings suggest that the outcome of D1 pharmacological manipulations might depend on the route of drug administration. The opposing effects of D1 antagonists when given either intra-NAc or systemically suggests a divergent effect of different D1 receptor-containing neurons in different brain areas for the establishment of a social hierarchy. Further studies are warranted to verify whether, indeed, D1 receptor activation in different brain areas exerts contrasting effects in social competitiveness.

In addition to the evidence reviewed above claiming for a role of D1 receptor function in social dominance, other studies support a role for D2 receptors. For example, dominant rats were shown to exhibit elevated D2/D3 receptor binding in the NAc shell and dorsal striatum as compared to subordinate rats (Jupp et al., 2016). Similarly, in humans and in monkeys, higher social status has been associated with higher striatal dopamine D2 receptor expression (Morgan et al., 2002, Martinez et al., 2010, Nader et al., 2012). Specifically, PET studies in humans using [^{11}C] raclopride revealed that dopamine D2/D3 receptor binding in the striatum positively correlated with a measure of social status (i.e., the Barratt Simplified Measure of Social Status) (Martinez et al., 2010), further supporting a role for D2-like receptors in social dominance. Both in macaques and in mice, pharmacological treatment involving systemic administration of a D2 receptor antagonist (sulpiride) reduced social dominance (Yamaguchi et al., 2017b). However, infusion of a dopamine D2 receptor agonist (quinpirole) into the NAc of rats, did not affect social dominance (van der Kooij et al. 2018a); again suggesting that the route of administration may be crucial for the ultimate effects of drugs targeting dopamine receptor function.

Thus, although collectively these studies confirm important roles for dopamine signaling in VTA-NAc circuitry in social dominance, the specific involvement of D1- versus D2- receptors and their neuronal pathways remain to be elucidated.

4. Inhibitory control of VTA dopamine neurons and the effects on social dominance

GABAergic interneurons comprise approximately 30% of the neurons within the VTA, where they exert inhibitory control onto VTA dopaminergic cells (Tan et al., 2011). Given the essential role of mesolimbic dopamine signaling in social dominance, compounds that affect GABAergic signaling in the VTA may thus be expected to affect social status as well. Benzodiazepines, for example, are used as anxiolytics and biochemically act as positive modulators for $GABA_A$ receptors. The addictive properties associated with benzodiazepine use have been thought to rely on disinhibition of GABAergic interneurons in the VTA, leading to enhanced dopamine signaling in the NAc (Tan et al., 2010). Congruent with the hypothesis that benzodiazepines may act in the VTA to enhance dopamine signaling, and thus boost social dominance, a recent study in rats showed that intra-VTA administration of diazepam i) reduces anxiety-like behaviors; ii) diminishes anxiety-related social submissiveness; and ii) increases dopamine levels in the NAc (van der Kooij et al. 2018a). In turn, the effects of intra-VTA diazepam administration on social dominance could be blocked by pre-infusion of a D1-receptor antagonist (SCH-23390) into the NAc (van der Kooij et al. 2018a). These findings suggest a critical role for $GABA_A$-mediated disinhibition of local VTA neurons, which through enhanced dopamine release in the NAc leads to a facilitation of social dominance in a competing individual.

A recent study has further supported a positive modulatory role of $GABA_A$ receptors in the VTA on the regulation of anxiety and social dominance. Specifically, intra-VTA infusion of the specific and potent $GABA_A$ receptor agonist, muscimol, in rats recapitulated the anxiolytic and social dominance-enhancing effects found after intra-VTA infusion of diazepam (see above; van der Kooij et al., 2018b). Conversely, intra-VTA infusion of the $GABA_A$ receptor antagonist bicuculline decreased social dominance and exerted anxiogenic actions (van der Kooij et al., 2018b). Regarding the potential mechanisms of action, it is important to note that muscimol had

opposite effects when infused either intra-NAc (Hollis et al. 2015), which caused a reduction in social dominance, or intra-VTA (van der Kooij et al. 2018a), which facilitated social dominance. This disparity was observed despite the fact that both treatments were equivalent in terms of dose and timing of injection. Thus, it is plausible that these differential muscimol effects rely on the differential neurochemistry and circuitry in each of the two brain regions. Thus, whereas dopaminergic neurotransmission in the VTA may be stimulated in response to GABAergic disinhibition by muscimol, NAc output would be restricted upon muscimol-mediated inhibition of MSNs.

Follow up pharmacological studies were aimed to delineate the precise $GABA_A$ receptor subtype in the VTA implicated in social dominance. $GABA_A$ receptors are heteropentameric structures often classified by the α-subunits expressed (Rudolph and Mohler, 2006). The biological functions of $GABA_A$ receptors depend on the specific α-subunits contained (Engin et al., 2018). Zolpidem is a benzodiazepine ligand that acts as an agonist on α1-subunit containing $GABA_A$ receptors, whereas TCS1105 is an agonist to α2-subunit containing $GABA_A$ receptors but acts antagonistic to $GABA_A$ receptors containing α1-subunits. Intra-VTA infusion of TCS1105 enhanced social dominance in rats whereas intra-VTA zolpidem was ineffective (van der Kooij et al. 2018b). Therefore, in the VTA, GABAergic mediated effects on social dominance appear to be mediated through α2-, rather than α1, subunit containing $GABA_A$ receptors.

Of special mention are the findings demonstrating that dopaminergic neurons in the VTA are, separately from local GABA-ergic neurons, also under direct inhibitory control by noradrenergic neurons from the locus coeruleus. Importantly, susceptibility to social defeat was found to be modulated by stimulation of these noradrenergic neurons (Isingrini et al. 2016).

5. Androgen receptors in social dominance

Androgen receptor signaling in the mesolimbic system comprises yet another molecular pathway through which social dominance may be affected. Levels of androgen steroid hormones tend to be higher for individuals

winning agonistic encounters as compared to those individuals at the losing end. This is the case, for example, in Mozambique tilapia fish (Oreochromis mossambicus) (Oliveira, 2009). Pharmacological treatment with the anti-androgen cyproteron acetate diminished the winning chances in previously dominant tilapias (note, however, that the chances of former losers were not improved by androgen supplementation) (Oliveira et al., 2009). Similarly, for the California mouse, winning territorial disputes in its home territory means that the chance of becoming dominant in future encounters is increased (Fuxjager et al., 2010). This snowball effect was matched by increased androgen receptor sensitivity in the VTA and NAc. Hence, these data implicate that the winning experience itself may affect central androgen signaling. Furthermore, the link between androgen signaling and social dominance is in line with the known role of androgens in territorial-related aggression (Kellam et al., 2006).

Conversion of testosterone into the potent androgen 5α-dihydrotestosterone is catalyzed by the enzyme steroid 5α-reductase 2 (5αR2). Intriguingly, 5αR2 knockout mice retain normal motor function, information processing and anxiety-like behavior, but show deficiencies in dominance-related behaviors as manifested by a lower aggression against intruders, impaired mating behavior and low social dominance in the tube test (Mosher et al., 2018). Interestingly, these 5αR2 knockout mice exhibit decreased D2 receptor binding in the NAc shell, thus 5αR2 could represent an important substrate for the regulation of dominance through the modulation of dopaminergic signaling in the mesolimbic system. However, this possibility remains to be determined.

6. Accumbal mitochondrial function and energy metabolism in social dominance

Recent work shows that metabolic processes –with a prominent role for mitochondrial function– within the NAc are critically related to the expression of social dominance. For instance, high anxious rats, that are prone to become subordinate during a social encounter with low anxious rats, exhibit impaired mitochondrial function in the NAc as compared with low anxious rats, as indicated by a lower mitochondrial respiratory capacity and ATP levels, while a higher ROS production (Hollis et al., 2015). Accordingly, pharmacological

studies have established a causal role for mitochondrial function in the establishment of social dominance in rats. Thus, intra-NAc microinfusion of very low doses of specific mitochondrial electron transport chain inhibitors (i.e., rotenone, an inhibitor of complex I function; malonic- and 3-nitroproprionic acid, inhibitors of complex II) reduced social rank, thereby recapitulating the low probability to become dominant displayed by high anxious animals. Conversely, intra-NAc infusion of nicotinamide, an amide form of vitamin B3 known to boost mitochondrial function, prevented the development of a subordinate status in high anxious rats (Hollis et al., 2015).

Strikingly, intra-VTA administration of the anxiolytic drug diazepam not only boosted mesolimbic dopamine function and social dominance (as discussed in section 4), mitochondrial function of the NAc was enhanced as well (van der Kooij et al., 2018a). Furthermore, the effects of diazepam intra-VTA infusion on social dominance were blocked by pre-infusion of the mitochondrial complex I inhibitor rotenone into the NAc (van der Kooij et al. 2018a). Thus, the effects of dopaminergic and GABAergic signaling in the VTA on social dominance are dependent on the engagement of mitochondrial function in the NAc. Moreover, these data imply that variations in NAc mitochondrial function (either natural or induced by life experiences such as, for example stress or pharmacological treatments) may affect individuals' propensity to become dominant or submissive. These data are further supported by a recent proton magnetic resonance spectroscopy (1H MRS) study which showed that subordinate mice from well-established colonies exhibit lower levels of energy-related metabolites in the NAc in comparison to dominant mice (Larrieu et al., 2017).

7. Other mesolimbic systems potentially implicated in social dominance

Imprinted genes, a class of genes showing monoallelic expression depending on the parent of origin, have gained significant attention in the mesolimbic regulation of social dominance. Specifically, transgenic Cyclin dependent kinase inhibitor 1c (Cdkn1c) mice exhibit a two-fold increase in Cdkn1c expression and display enhanced social dominance. In agreement with the central role of dopamine for social dominance as discussed above, transgenic Cdkn1c mice possess an altered expression of dopamine system-related genes, causing

increased levels of tyrosine hydroxylase and striatal dopamine (McNamara et al., 2018).

In addition to the integral contributions of abovementioned neurotransmitters, hormones and imprinted genes, a top-down approach, scrutinizing the external factors that impinge on social dominance, could also improve our understanding of the neurobiological mechanisms underlying social hierarchy formation. Stress and social hierarchies, for example, are intimately linked. Stress drives rats to attain a low social rank and solidifies the establishment of this social hierarchy (Cordero and Sandi, 2007). Housing rats in a VBS is highly stressful and social hierarchies are readily formed. Interestingly, after VBS-exposure, subordinate rats exhibited increased D2 receptor levels in the NAc, as compared to controls (Lucas et al., 2004). In contrast, D1 receptor binding in the NAc was not affected in VBS-exposed rats. These results suggest that D2 receptor expression may be linked to stress-induced submissive behavior.

Peripheral levels of glucocorticoid concentrations have been linked to the establishment of social rank although the direction of this relationship is complex (Creel, 2001; Hardy et al. 2002; Timmer and Sandi, 2010). Brain-specific manipulations demonstrated that an intracerebroventricular corticosterone injection given to a submissive rat facilitated the long-term maintenance of the social status (Weger et al. 2018). However, NAc-specific corticosterone injections failed to reproduce these effects, suggesting that glucocorticoid facilitation of social subordination may involve other brain regions or the concerted actions of several neural circuits (Weger et al. 2018). Importantly, following chronic social defeat, expression levels of multiple genes involved in glucocorticoid signaling were changed in the NAc, including an upregulation of the glucocorticoid receptor (Sachs et al. 2018). Additionally, putative glucocorticoid actions in the NAc could modulate social dominance directly through mesolimbic dopamine signaling. Thus, chronic stress was previously found to instill social aversion specifically through brain dopaminoceptive neurons expressing glucocorticoid receptors (Barik et al. 2013). Nonetheless, a direct role for glucocorticoids to modulate social hierarchy formation through mesolimbic mechanisms remains to be established.

Whether stress modulates social dominance by affecting the synaptic function in the mesolimbic system

requires further investigation, but indirect evidence supports this possibility. Neuroligin-2 is a cell adhesion molecule associated with GABAergic synapses (Chih et al., 2005) and expression levels are reduced following chronic restraint stress (van der Kooij et al., 2014). A recent study showed a reduction of neuroligin-2 levels on D1, but not D2, receptor positive cells in the NAc of mice exposed to social defeat stress (Heshmati et al., 2018). Relevant herein is the demonstration that enhancing the activity of the MSNs containing the D1, but not D2, receptor promoted resilience after chronic social defeat stress (Francis et al., 2015). Congruent with the reported role for accumbal D1 receptors in social dominance (see above) and the link between neuroligin-2 and stress-resilience is the finding that neuroligin-2 knockdown in D1 receptor-containing cells in mice promoted subordination and stress susceptibility (Hashmati et al. 2018). These findings may also be relevant to humans since accumbal neuroligin-2 gene expression was reduced in patients with major depressive disorder (Hashmati et al. 2018). Interestingly, the relationship between stress and social dominance appears to operate in both directions since a recent report showed that the social status of mice predicted the impact of a social stressor as well (Larrieu et al. 2017; Larrieu and Sandi, 2018). This connection was associated with the NAc metabolic profile (Larrieu et al. 2017), again accentuating the involvement of the mesolimbic system in social hierarchy formation.

8. Concluding remarks and future directions

Here, we have reviewed accumulating evidence indicating that the mesolimbic system and associated circuits play a key regulatory role in social dominance behavior. According to the reviewed findings, while the VTA acts as a decisive hub integrating a myriad of modulatory mechanisms impinging in social dominance, the NAc represents a critical effector region. At the neuropharmacological level, GABAergic signaling in the VTA and dopaminergic signaling in the NAc emerge as central regulators of social status. One remaining issue for the field will be to identify the specific cell types and effector circuitries involved in both the VTA and NAc. In that respect, we cannot exclude that the VTA may also function as an effector brain region of social dominance under certain conditions, nor that the NAc may embody modulatory functions concerning social dominance.

As discussed in section 7, hormonal actions in the VTA represented by the androgen receptor system may also mediate (territorial) dominance. Findings in the 5αR2 knockout mice have coupled androgen function back to mesolimbic dopamine signaling. These interesting findings call for putative effects of other hormone receptor systems on social dominance, especially since studies in rodents have indicated alterations in reward thresholds under the influence of the ovarian hormones estrogen and progesterone (Bless et al., 1997). Unfortunately, the possible effects of female steroid hormones on social dominance have not been investigated, as animal work on social dominance almost exclusively deals with male subjects. The lack of attention to female social dominance in this field of research may partially stem from the frequently argued limited or absence of inter-female aggression in rodents. However, further studies are needed to examine female dominance, as several possibilities to increase female aggression in rodents have been identified [e.g., through the application of male odorants to female intruders (Harris et al., 2018) or by examining behavior against intruders in lactating dams (Jacobson-Pick et al., 2013)].

Several genes have been linked to personality traits that facilitate social dominance; as such, social status may have a hereditary basis (van der Kooij and Sandi, 2015). Appealing therefore are the recent data linking elevated Cdkn1c expression, equivalent to loss-of-imprinting, to alterations in dopamine and increased motivation for reward and social dominance, as these tap into the known involvement of the mesolimbic dopamine system on social hierarchies.

In conclusion, mesolimbic dopamine signaling and its effector circuitries emerge as a fundamental system for the establishment of social hierarchies. Neuropharmacological progress in this field is expected to contribute to ameliorating social dysfunctions and associated impairments in mental health.

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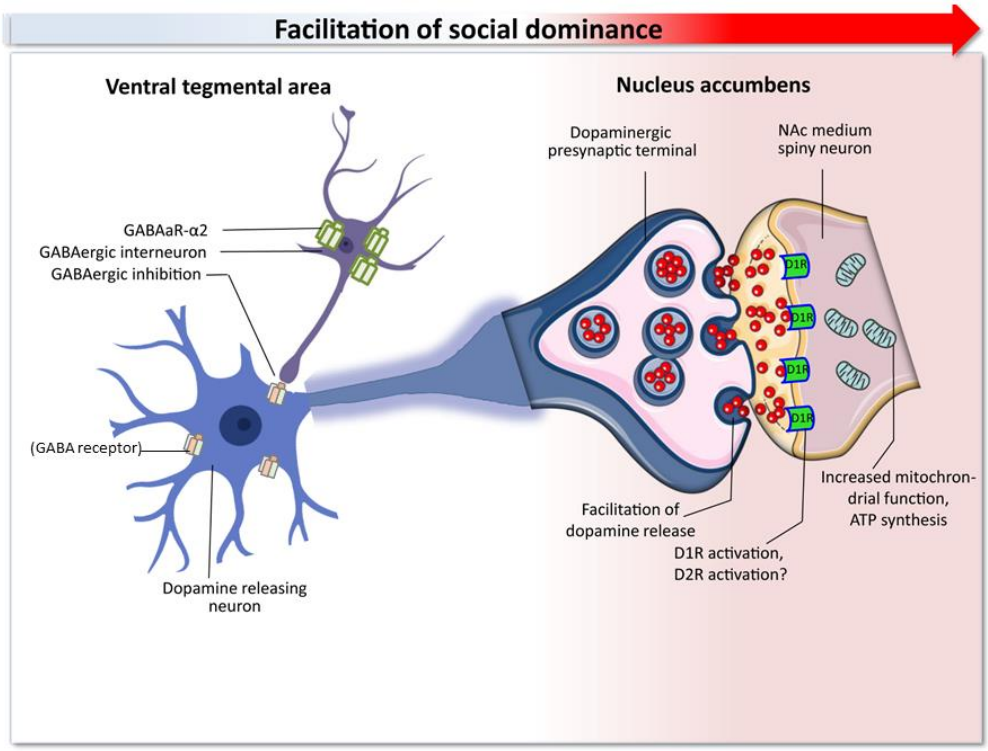

Figure 1. Scheme illustrating the hypothesized mechanisms whereby the mesolimbic system and associated circuits regulate social dominance. Dopaminergic neurons in the VTA project mainly to the NAc. The dopaminergic projection neurons are under inhibitory control by GABAergic interneurons through which these neurons moderate dopamine release into the NAc. Disinhibition of VTA interneurons leads to enhanced dopamine (DA) neurotransmission in the NAc, which in turn has been associated with enhanced social dominance (figure is modified and updated from van der Kooij et al. 2018a). Recent findings suggest that modulation of social dominance through GABAergic mechanisms in the VTA are mediated by the $GABA_A$ α2 subunits (van der Kooij et al. 2018b). Since increased mesolimbic DA signaling has been associated with enhanced social dominance, $GABA_A$ α2 subunit-containing receptors may be centrally involved in the GABAergic mediated disinhibition which stimulates DA release onto NAc terminals. During social competition, enhanced DA release in the NAc activates dopamine D1 and possibly D2 receptors. D1 activation in the NAc has been linked to enhanced mitochondrial function, in turn involved in enhanced social dominance. Other mediators

associated with the mesolimbic system, including androgen receptors, stress, and genetic factors also play important roles in social dominance (not depicted here).